TABLE 3.4.4.14 (continued)
CARCINOGENICITY STUDY IN RATS: INCIDENCE OF PRIMARY NEOPLASMS

Histopathological finding		Dose level (mg/kg/day)									
ORGAN SYSTEM		0		0		3		15		100	
Organ/Tissue	TD	Group 0		Group 4		Group 1		Group 2		Group 3	
Neoplasm		Ad lib diet		Restricted diet		Low Dose		Mid Dose		High Dose	
		m	f	m	f	m	f	m	f	m	f
		50	50	50	50	50	50	50	50	50	50
HEMATOPOIETIC/LYMPHOID SYSTEM											
Generalized tumors		50	50	50	50	50	50	50	50	50	50
Lymphoma	MA	0	0	2	1	0	0	1	0	0	0
Histiocytic sarcoma	MA	1	1	1	0	2	0	0	0	0	0
Thymus		50	49	48	49	48	48	44	49	49	50
Thymoma, benign	BE	9	5	9	8	5	7	7	5	9	3
Thymoma, malignant	MA	1	0	0	0	0	0	0	0	0	0
Carcinosarcoma	MA	1	0	0	0	0	0	0	0	0	0
Lymph node (all sites)		50	50	50	50	50	50	50	50	50	50
Lymphangioma	BE	0	0	0	0	0	1	0	0	0	0
HEPATOPANCREATIC SYSTEM											
Liver	BE	49	50	50	50	50	50	50	50	50	50
Hepatocellular adenoma	MA	1	1	2	0	3	1	4	0	2	2
Hepatocellular carcinoma	BE	2	0	0	0	3	0	3	0	1	0
Bile duct adenocarcinoma	MA	0	0	0	0	0	0	1	0	0	0
Pancreas		50	50	50	50	50	50	49	50	50	49
Islet cell adenoma	BE	0	0	2	2	2	0	2	1	3	0
Acinar cell adenoma	BE	0	0	1	0	0	0	0	0	0	1
INTEGUMENTARY SYSTEM											
Skin		50	50	50	50	50	50	50	50	50	50
Keratoacanthoma	BE	2	1	0	1	4	1	1	0	2	0
Trichofolliculoma	BE	2	0	1	0	1	0	0	0	0	0
Eyelid adenoma	BE	0	0	1	0	0	0	0	0	0	0
Sebaceous adenoma	BE	1	0	0	0	0	0	0	0	0	0
Fibroma	BE	1	3	0	0	0	0	1	0	0	0
Lipoma	BE	1	0	0	0	0	0	1	1	0	0
Sebaceous carcinoma	MA	0	0	0	0	0	0	0	0	1	0
Basosquamous carcinoma	MA	0	1	0	0	0	0	1	0	0	1
Liposarcoma	MA	0	0	0	0	0	0	1	0	0	0
Malig. fibrous histiocytoma	MA	0	0	1	0	0	0	0	0	0	1
Mixed tumor	MA	0	0	0	1	0	0	0	0	0	0
Mammary gland			49		49		49		49		50
Fibroadenoma	BE		8		8		6		9		10
Adenoma	BE		1		1		0		2		1
Adenocarcinoma	MA		2		1		2		3		5
RESPIRATORY SYSTEM											
Lungs		50	50	50	50	50	50	50	50	50	50
Bronchiolar/alveolar adenoma	BE	0	1	1 •	1	0	0	1	0	2	2
Bronchiolar/alveolar carcinoma	MA	1	0	0	0	0	0	0	0	0	0

Tumor Designation: BE: Benign; MA: Malignant
No statistically significant increases or decreases in tumor frequency compared to control 1 or control 2 ($p \leq 0.05$)
The numbers in each row against an organ/tissue indicate the number of animals examined.

TABLE 3.4.4.14 (continued)
CARCINOGENICITY STUDY IN RATS: INCIDENCE OF PRIMARY NEOPLASMS

Histopathological finding		Dose level (mg/kg/day)									
ORGAN SYSTEM	TD	0		0		3		15		100	
Organ/Tissue		Group 0		Group 4		Group 1		Group 2		Group 3	
Neoplasm		Ad lib diet		Restricted diet		Low Dose		Mid Dose		High Dose	
		m	f	m	f	m	f	m	f	m	f
		50	50	50	50	50	50	50	50	50	50
CIRCULATORY SYSTEM											
Hemangioma		50	50	50	50	50	50	50	50	50	50
All sites	BE	9	1	6	1	8	1	8	2	10	2
Spleen		1	1	1	1	2	0	1	1	1	1
Lymph node		5	0	4	0	6	0	6	0	9	1
Adrenal gland (adjac. tissue)		0	0	0	0	0	0	1	0	0	0
Spinal cord		1	0	0	0	0	0	0	0	0	0
Bone / sternum / knee		2	0	1	0	0	0	0	0	0	0
Uterus			0		0		1		1		0
Hemangiosarcoma		50	50	50	50	50	50	50	50	50	50
All sites	MA	2	0	0	0	2	1	4	2	1	0
Spleen		2	0	0	0	2	0	0	0	1	0
Lymph node		0	0	0	0	0	0	3	0	0	0
Uterus			0		0		0		2		0
Ovary			0		0		1		0		0
Heart		0	0	0	0	0	0	1	0	0	0
MALE REPRODUCTIVE TRACT											
Testis		50		50		50		49		50	
Leydig cell tumor	BE	19		16		19		18		16	
FEMALE REPRODUCTIVE TRACT											
Ovary			50		50		50		50		50
Sex cord stromal tumor	BE		3		4		4		2		5
Granulosa cell tumor	BE		0		0		0		1		0
Granulosa / theca cell tumor	BE		0		0		1		0		0
Granulosa / theca cell tumor	MA		0		1		0		0		0
Theca cell tumor	BE		0		1		0		0		1
Theca cell tumor	MA		0		0		1		0		0
Sertoli cell tumor	BE		0		0		1		1		0
Lipoma	BE		0		1		0		0		0
Uterus			50		50		50		50		50
Squamous cell carcinoma	MA		1		1		0		0		0
Adenocarcinoma	MA		1		0		1		0		0
Endometrial stromal sarcoma	MA		3		2		3		1		1
Vagina			50		50		50		50		50
Endometrial stromal sarcoma	MA		2		1		0		1		1
URINARY SYSTEM											
Kidney		50	50	50	50	50	50	50	50	50	50
Tubular adenoma	BE	1	1	0	0	0	1	4	1	2	2
Lipomatous tumor (lipoma)	BE	0	0	0	0	0	0	1	0	0	0
Urinary bladder		50	49	50	50	50	50	50	50	50	50
Transitional cell carcinoma	MA	2	0	1	0	0	0	0	0	0	0

Tumor Designation: BE: Benign; MA: Malignant
No statistically significant increases or decreases in tumor frequency compared to control 1 or control 2 ($p \leq 0.05$)
The numbers in each row against an organ/tissue indicate the number of animals examined.

TABLE 3.4.4.14 (continued)
CARCINOGENICITY STUDY IN RATS: INCIDENCE OF PRIMARY NEOPLASMS

Histopathological finding		Dose level (mg/kg/day)									
ORGAN SYSTEM		0		0		3		15		100	
Organ/Tissue	TD	Group 0		Group 4		Group 1		Group 2		Group 3	
Neoplasm		Ad lib diet		Restricted diet		Low Dose		Mid Dose		High Dose	
		m	f	m	f	m	f	m	f	m	f
		50	50	50	50	50	50	50	50	50	50
MUSCULOSKELETAL SYSTEM											
Femur		50	50	50	50	50	50	50	50	50	50
Osteosarcoma	MA	1	1	0	0	0	0	0	0	1	0
NERVOUS SYSTEM											
Brain		50	50	50	50	50	50	50	50	50	50
Granular cell tumor	BE	2	2	2	0	0	0	0	0	1	0
Spinal cord		50	50	50	50	50	50	50	50	50	50
Granular cell tumor	BE	1	0	0	0	0	0	0	0	0	0
Schwann cells (all sites, excl. heart)											
Benign schwannoma	BE	0	0	1	0	1	0	0	0	0	0
Malignant schwannoma	MA	0	1	1	0	0	1	0	0	0	0
Heart: Malignant schwannoma	MA	1	0	1	0	0	0	0	0	0	0
BODY CAVITIES*		3	1	3	2	2	1	3	1	4	0
Lipoma	BE	1	0	1	1	0	0	1	0	0	0

Tumor Designation: BE: Benign; MA: Malignant
No statistically significant increases or decreases in tumor frequency compared to control 1 or control 2 ($p \leq 0.05$)
The numbers in each row against an organ/tissue indicate the number of animals examined unless marked by an asterisk (*).
*: Number of animals with macroscopic findings (histopathological investigation conducted only for these animals)

Toxicokinetics: Plasma concentrations of telmisartan increased with the dose in a more than proportional manner in the morning and increased proportionally with the dose in the afternoon. The higher plasma concentration in the morning was due to higher food (and, consequently, drug) intake of the rats at night time than at day time. Between 3 months and 24 months, group mean AUC values increased by a factor of 1.3 to 2.5, which, according to the sponsor, indicates a decrease in clearance with increasing age (Table 3.3.4.15). However, a high individual variability in the data may preclude drawing such a general conclusion. The rats appear to have been adequately exposed to telmisartan since in healthy human volunteers a dose of 120 mg telmisartan (protocol #502.124) resulted in $AUC_{0\text{-}24hr}$ of 2.04 (male) and 2.38 (female) µg.h/ml, whereas the high dose of 100 mg/kg/day in rats resulted in a mean $AUC_{0\text{-}24hr}$ which exceeded the human therapeutic AUC value by a factor of approximately 210 (males) or 116 (females).

The AUC values were calculated from the mean of two plasma concentrations taken at 8 a.m. and 4 p.m. and multiplied by 24 hr.

$$AUC_{0\text{-}24h} = \tfrac{1}{2} (C_{8\ a.m.} + C_{4\ p.m.}) \cdot 24\ h$$

TABLE 3.3.4.15
104 WEEK CARCINOGENICITY STUDY IN RATS. TOXICOKINETICS

Time	Arithmetic mean plasma concentrations (µg/ml) and AUC (µg·h/ml)					
	3 mg/kg		15 mg/kg		100 mg/kg	
	Males	Females	Males	Females	Males	Females
Month 3						
AUC_{0-24h}	2.17	2.33	14.01	13.39	162.12	137.80
$C_{8\ a.m.}$	0.1	0.13	0.76	0.69	7.38	7.61
$C_{4\ p.m.}$	0.08	0.07	0.41	0.43	6.14	3.87
Month 6						
AUC_{0-24h}	2.50	2.44	13.70	15.34	156.05	221.92
$C_{8\ a.m.}$	0.14	0.13	0.79	0.89	10.65	15.51
$C_{4\ p.m.}$	0.07	0.07	0.36	0.39	2.35	2.98
Month 12						
AUC_{0-24h}	3.28	3.69	22.80	22.75	176.00	240.02
$C_{8\ a.m.}$	0.16	0.22	1.29	1.20	11.42	14.12
$C_{4\ p.m.}$	0.11	0.09	0.61	0.47	3.24	5.88
Month 24						
AUC_{0-24h}	3.83	5.53	24.52	18.04	428.18	276.43
$C_{8\ a.m.}$	0.19	0.35	1.37	0.97	18.67	18.43
$C_{4\ p.m.}$	0.13	0.12	0.67	0.54	15.53	4.61

In summary, telmisartan was given to rats as a dietary admixture at doses of 3, 15 and 100 mg/kg/day for 104 weeks. There were no demonstrable clinical signs of toxicity or effects on survival. Systolic blood pressures were significantly lower at 3 and 6 months in the lower dosage groups, and at 3, 6, 12 and 18 months in the mid and high dosage groups (maximum effect achieved at the intermediate dose level- 26 to 41%, depending on week of measurement). Group mean body weights of males given 15 and 100 mg/kg/day were significantly lower (4 to 13% and 7 to 15%, respectively) than the mean weight of control 2 males over most of the study period. However, the body weight differences between treated and control groups at termination were less pronounced (-7 and -9%) and not statistically significant. Although females given 15 and 100 mg/kg/day had significantly lower (than control 2) body weights (7 and 5%, respectively) by study week 12, thereafter the differences were less pronounced, and after week 36, no longer significant. At termination of the study, body weights of treated female groups were 2.7 to 5.6% higher ($p > 0.05$) than the weight of the control 2 group. Red blood cell indices decreased approximately 10% in high dose males (no change in treated females). Treatment-related biochemical changes were most pronounced in mid and high dose males. Significant, but not dose-related, increases in blood urea nitrogen (128 and 138% in males, and 29 and 71% in females) and creatinine (significant only in males, 25% at mid and high doses) relative to control 2 animals were observed in mid and high dose groups. Total bilirubin was increased in high dose male (94%) and female (93%) rats compared to control 2 animals. At necropsy, significant but non dose-related decreases (14-24%) in absolute and relative heart weights relative to the diet restricted control were noted in males at all doses. Absolute and relative kidney weights were significantly reduced (11-14%) in both sexes at 15 and 100 mg/kg/day.

Non-neoplastic histopathology considered to be related to treatment was seen in the kidneys, gastric mucosa, thymus and lymph nodes. Thickening of intralobular renal arteries, an extension of JGA hypertrophy and hyperplasia, and renal cysts were observed in a dose-dependent manner in animals of both sexes at 15 or more mg/kg/day. Gastric mucosal injury, manifested as erosions and ulcers, was observed in both sexes at 15 or 100 mg/kg/day (incidence was higher in the 15 mg/kg/day dose group). Increased incidences of thymic atrophy in high dose males and cystic ectasia of lymph nodes in mid and high dose males are attributed by the sponsor to body weight gain suppression in these groups. Plasma concentrations of telmisartan increased with dose in a more than proportional manner. Based on the mean AUC values for telmisartan, the systemic exposure at the high dose of 100 mg/kg/day in the male and female rat exceeds the systemic exposure in humans (at a clinical dose of 120 mg) by factors of 210 and 116, respectively. These observations, along with reduced body weight gain and increased BUN values in mid and high dose males, lead us to conclude that 100 mg/kg/day was an appropriate high dose for the study. Both the sponsor's and the FDA's analyses revealed no statistically significant increased trend in the incidence of any neoplasm that could be attributed to treatment with telmisartan for rats of either sex that survived the treatment period or were killed or died during the treatment period.

3.4. ***Mutagenicity Studies***

3.4.1. Ames Assay (Report #U94-2019, Study #Gen/Tox20/93) Vol. 40

This GLP study was conducted by between October 12 and November 19, 1993.

The Ames test permits the detection of gene mutations (base pair substitutions, frameshift mutations) induced by the test compound or its metabolites in histidine-requiring strains of *Salmonella typhimurium* and a tryptophan-dependent strain of *Escherichia coli*. In the presence of a genotoxic agent, tester strains revert from histidine/tryptophan dependence (auxotrophy) to histidine/tryptophan independence (prototrophy). Telmisartan (batch #8350071) was evaluated for its ability to increase the reversion frequency at the histidine locus in *Salmonella typhimurium* strains, TA1535, TA100, TA 102 (sensitive to base-pair substitution) and TA1537, TA 98 (susceptible to frameshift mutagens). Assays were performed with and without metabolic activation by addition of microsomal enzymes (S-9 mix) derived from livers of Arochlor 1254 (500 mg/kg) treated rats and hamsters. The reference positive controls used were: sodium azide, 2-nitrofluorene, mitomycin C (in the absence of S-9 mix) 2-aminofluorene, , 2-aminoanthracene, cyclophosphamide, and 1,8-dihydroxy-anthraquinone (in the presence of S-9 mix). The negative control was DMSO. The concentration levels tested were based on the results of a previous non-GLP study in which concentrations of 10 to 2500 µg/plate did not increase the number of his+ revertant colonies in any of the 4 Salmonella strains tested or the number of try+ revertant colonies in the E. coli strain, with or without metabolic activation. At concentrations of 1000 µg or more/plate, a moderate decrease in absolute revertant numbers was evident, with no thinning of background lawn, indicating bacteriotoxicity.

In the mutation assay, telmisartan was dissolved in dimethylsulfoxide and tested at concentrations of 10 to 2500 µg/plate in triplicate. The test substance precipitated at the highest concentration levels (1000 and 2500 µg/plate). A microbial toxicity, as seen by a reduced background lawn or a decrease of absolute revertant numbers, was observed at doses of 1000 or more µg/plate with all bacterial strains, both in the presence and absence of metabolic activation. For all strains, exposure to telmisartan resulted in revertant frequencies similar to those observed in the concurrent solvent control cultures. Addition of liver homogenates had no influence on mutation induction. All positive and negative control values were within acceptable limits. It is concluded that telmisartan had no genotoxic activity in this assay.

3.4.2. *In vitro* Gene Mutation Test With Chinese Hamster V79 Cells
(Report #U94-2004; Study #Gen Tox 15/93) Vol. 40

This GLP study was conducted by[redacted] between June 24 and October 5, 1993.

The Chinese Hamster V79 cell assay system detects mutations (base pair substitutions, frameshifts, deletions and chromosomal rearrangements induced by the test substance) from the parental type to the mutant form which give rise to a change in an enzymatic protein, HGPRT (hypoxanthine guanine phosphoribosyl transferase). The gene for HGPRT is located on the X chromosome and the role of the HGPRT enzyme is to induce the biosynthesis of purine nucleotides by converting hypoxanthine and guanine to the corresponding nucleoside 5'-monophosphate. Purine analogues such as 6-thioguanine (6-TG) are also converted, but to toxic ribonucleotides, which kill cells with normal enzyme activity. Conversely, mutant cells with a HGPRT-deficient genotype due to a mutation induced by a genotoxic agent can proliferate in a medium containing 6-thioguanine because of their ability to synthesize that required purine via the *de novo* pathway from 5'-ribose phosphate, amino acids and ATP. Experimentally, mutagenic effects are manifested by the appearance of cells resistant to 6-thioguanine (6-TG) and can be quantified by comparison of the numbers of 6-TG resistant colonies in the treated and control cultures. The experiment was conducted both in the presence and absence of rat-liver postmitochondrial fraction S-9 (prepared from rats injected with Aroclor 1254) and co-factors in order to ensure that any mutagenic effect of metabolites of the test compound would also be detected.

Two independent experiments were performed under the same experimental conditions with the same batch of telmisartan (batch #8230231).

V-79 cell cultures (male Chinese hamster lung cells) were exposed (for 3 hr) to the following concentrations of telmisartan in DMSO: 10, 50, 75 and 100 µg/ml. The positive control used in the non-activated part of the experiment was ethylmethansulfonate (500 µg/ml). In the presence of rat liver S-9 mix, 7,12-dimethylbenzanthracene (7.5 and 10 µg/ml) was used. An untreated cell culture and a solvent (DMSO) control were included in each mutation assay. V-79 cell populations were in exponential phase of growth irrespective of treatments. Subcultures of each culture were prepared to maintain exponential growth. After 5 days, colonies were stained and counted. During this period cells could recover and divide to express the mutant phenotype. The number of colonies which developed in these cultures reflected the viability at the end of treatment. The high density cultures were subjected to the mutant selection procedure by supplementing the growth medium with 10 µg/ml 6-TG. Only cells mutated at the HGPRT locus could survive the 6-TG treatment. The number of colonies formed in the petri dishes during 6 days of incubation at 37 C reflected the overall number of mutations induced by the treatment with the test substance or the mutagen (i.e. positive control). The mutant colonies were counted manually and the mutant frequency is expressed as the number of 6-TG resistant mutants/million viable cells for each concentration. All comparisons were made against the concurrent vehicle control.

Results: In all experiments there was good cellular growth. Telmisartan was cytotoxic at concentrations above 50 µg/ml with metabolic activation (survival about 70% at 75 µg/ml and about 23% at 100 µg/ml) and without metabolic activation (survival about 40% at 75 µg/ml and about 5% at 100 µg/ml).

No dose-related increase in total mutant clones and mutant frequencies was observed with varying concentrations of telmisartan in the absence of metabolic activation. The mutant frequencies varied between 0 and $16.8/10^6$ viable cells ($16.8/10^6$ at a concentration of 100 µg/ml in one experiment, $0/10^6$ at the same concentration in the other) compared to concurrent control values (3.6 or $9.4/10^6$ cells) and were within the laboratory's historical control range (mean $6.9/10^6$, range 0-$35.2/10^6$ viable cells) (Table 3.4.2.1). Thus, the data were evaluated as clearly negative. In contrast, the positive control EMS induced a mutation frequency which was clearly in excess of the background.

TABLE 3.4.2.1
MUTAGENIC ACTIVITY OF TELMISARTAN IN V79 CELLS WITHOUT METABOLIC ACTIVATION

Compound (µg/ml)	% Survivors		HPRT Mutants/10^6 Survivors	
	Experiment 1	Experiment 2	Experiment 1	Experiment 2
Negative Control DMSO	100.0	100.0	3.6	9.4
Positive Control EMS 500	98.6	83.2	137.5*	101.0*
Telmisartan				
10	108.6	96.1	0.5	5.9
50	100.0	97.7	2.5	9.3
75	46.8	34.1	0	2.2
100	4.7	5.0	0	16.8

* Statistically significant increase ($p \leq 0.05$)

In the presence of metabolic activation, telmisartan, in the initial experiment, was associated with mutant frequencies (0 to $4.3/10^6$ viable cells) close to the concurrent control frequency ($1.6/10^6$ viable cells). However, in the repeat experiment a statistically significant ($p < 0.05$) increase in mutation frequency was observed at 75 µg/ml ($27.1/10^6$ *versus* concurrent control frequency of $15.1/10^6$) (Table 3.4.2.2). Since this increase was not concentration-dependent and within the range of the laboratory's historical control data (mean $6.6/10^6$, range 0-$35.2/10^6$ viable cells), the sponsor concludes that telmisartan has no genotoxic activity in this assay whether in the presence or absence of S-9 mix. The positive control, DMBA, significantly and consistently increased mutant frequencies in both studies.

TABLE 3.4.2.2

MUTAGENIC ACTIVITY OF TELMISARTAN IN V79 CELLS WITH METABOLIC ACTIVATION

Compound (µg/ml)	% Survivors		HPRT Mutants/10^6 Survivors§	
	Experiment 1	Experiment 2	Experiment 1	Experiment 2
Negative Control				
DMSO	100.0	100.0	1.6	15.1
Positive Control				
DMBA				
10	0.5	-	138.6*	-
7.5	-	8.0	-	249.3*
Telmisartan				
10	103.4	104.6	0	22.2
50	93.0	93.7	1.6	11.0
75	70.5	70.1	4.9	27.1*
100	19	27.8	4.3	20.4

* Statistically significant increase ($p \leq 5\%$)

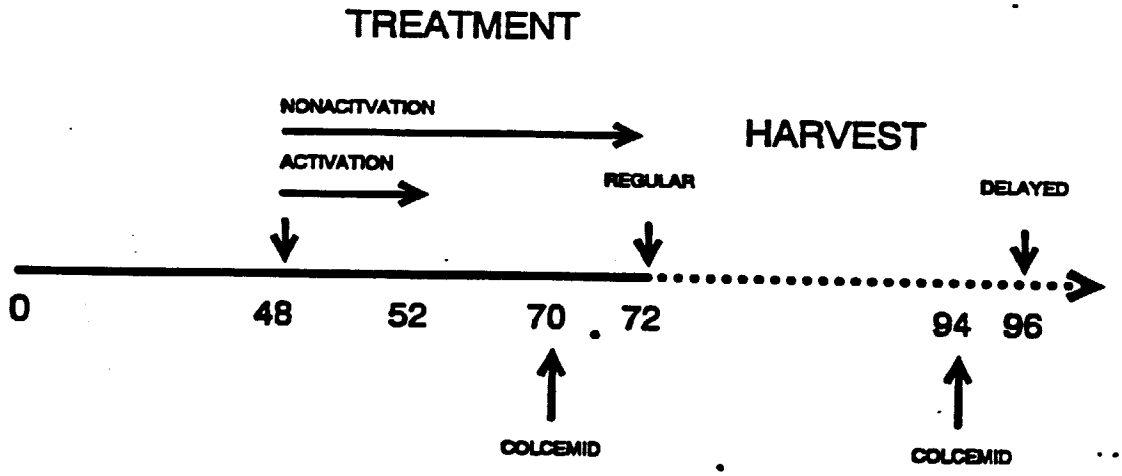
§ Historical data: mean: 6.6; range: 0 to 35.2/10^6

3.4.3. *Vitro* Chromosomal Aberration Test in Human Lymphocytes (Report #U94-2086; Study #Gen Tox 06/92) Vol. 41

This GLP study was conducted by[ ]between February 24 and April 23, 1993.

Methods: Two human lymphocyte cultures were prepared from blood taken from two different donors (sex not identified). Lymphocytes were induced to divide in culture by mitogen phytohemagglutinin A for 48 hr. After the incubation period, solvent (DMSO), positive control or telmisartan (batch #WE810110 or 8350071) was added with or without exogenous metabolic activation (S-9 fraction from Aroclor 1254-induced rat liver). Positive controls were adriamycin (0.05 or 0.075 µg/ml) and cyclophosphamide (28 or 42 µg/ml) in the absence and presence of S-9 mix, respectively. Test substance (concentration levels ranging from 10 to 200 µg/ml) was added to the cultures in the presence or absence of a metabolic activation system.

Cells were exposed to telmisartan or positive control in the absence and presence of S-9 mix for 24 and 4 hr, respectively. In the assay without metabolic activation, 22 hr after the beginning of treatment, i.e., 2 hours before harvesting the cells (at 70th hour), colcemide was added (0.2 µg/ml) to arrest dividing cells in metaphase. Cultures treated with S-9 mix were incubated for 4 hr with telmisartan or positive control (treatment was limited to 4 hr due to toxic effects of S-9 mix on the cells). At the end of incubation (i.e., at 52nd hr), the cells were washed three times and incubated for a further 18 hr. At 70th hr, colcemide was added and the cells harvested 2 hr after the addition of colcemide. At the end of 24 hr (i.e., at 72nd hour in both cases), cultures were centrifuged, cells suspended, spread on slides and stained. The cells were examined under the microscope and screened for chromosome abnormalities (gaps, breaks, translocations, etc.). In the repeat experiments for all controls and high dose cultures, colcemid was added at 94 hr (instead of 70 hr) and the cells harvested at 96 hr (instead of 72 hr). Duplicate cultures with one hundred cells/culture were analyzed per concentration. The mitotic index was evaluated from 1000 cells per experimental point.



Treatment Schedule in Hours

Test	Culture Initiation	Treatment	Colcemid	Harvesting	
				Regular	Delayed
- S9	0	48 - 72	70 (94)	72	96
+ S9	0	48 - 52	70 (94)	72	96

In parallel cultures treated with the control and telmisartan, cell proliferation kinetics was monitored in the presence and absence of metabolic activation by 5-bromo-2-deoxyuridine labelling followed by a modified fluorescent plus giemsa staining.

The clastogenic potential of the test compound was evaluated by determining the percentage of cells showing structural chromosomal aberrations (excluding gaps). A positive response was defined as a reproducible and concentration-dependent increase in the aberration frequency in the exposed cultures.

Results: A concentration-dependent decrease in the mitotic index of human lymphocytes was observed in cultures treated with telmisartan in the absence of S-9 mix. At concentrations between 10 and 50 µg/ml there was a slightly reduced mitotic index (96 to 85%). A relatively high cytotoxicity of telmisartan was demonstrated in the absence of S-9 mix where mitotic index at 125 and 250 µg/ml decreased to 45% and 19%, respectively, of solvent control. In the repeat experiment (in the absence of S-9 mix), with blood from another donor, telmisartan at concentrations of 100 to 200 µg/ml resulted in 72 to 93% mitotic inhibition compared to the control (Table 3.4.3.1). In the activation system, the mitotic activity fell to approximately one-half at a concentration of 125 µg/ml, the highest concentration tested in experiment 1. At the delayed harvest the toxicity was less pronounced, indicating a recovery effect. In contrast to what was seen in the absence of S-9 mix, when tested in the presence of S-9 mix, telmisartan at concentrations of 10 and 50 µg/ml showed no signs of reduced mitotic activity. The repeat experiment (expt. 2) performed in the presence of the metabolic activation system showed a decrease of the mitotic activity to 58% at the highest dose level of 200 µg/ml (negative control 100%). At the delayed harvest a treatment-related depression of mitotic index (MI 61%, control 100%) was still evident at 200 µg/ml (Table 3.4.3.2).

TABLE 3.4.3.1
CHROMOSOMAL ABERRATIONS STUDY: EFFECTS ON MITOTIC INDEX (WITHOUT METABOLIC ACTIVATION)

Test Substance (µg/ml)	Experiment 1				Experiment 2				Experiment 3			
	MI	% Δ	TOX	Eval	MI	% Δ	TOX	Eval	MI	% Δ	TOX	Eval
	Regular Harvest											
-Control (DMSO)	121	-	NT	x	61	-	NT	x	51	-	NT	x
+Control (ADR)												
0.05	134	+9.7	NT	x	54	-11	NT		47	-8	NT	x
0.075					50	-18	NT	x				
Telmisartan												
2	130	+6.9	NT						55	+8	NT	
10	96	-21	NT	x	48	-21	NT	x	34	-43	LT	x
50	85	-30	LT	x	33	-46	LT	x	22	-57	HT	b
75									20	-61	HT	b
100					7	-88	HT	x	30	-41	LT	b
125	45	-63	HT	x					16	-69	HT	b
150					17	-72	HT	a	8	-84	HT	
200					4	-93	HT	b				
250	19	-84	HT	b								
500 (P)	4	-97	HT	b					0		HT	
	Delayed Harvest											
-Control (DMSO)					58	-	NT	x				
+Control (ADR)												
0.05					52	-10	NT	x				
Telmisartan												
100					30	-48	LT					
150					44	-24	NT	x				
200					4	-93	HT	b				

% Δ Percent change compared to DMSO control
x 100 cells/culture scored
a < 100 cells/culture scored (toxic)
b < 50 cells/culture scored (toxic)

NT No toxicity (MI 75 to 100% of control)
LT Low toxicity (MI 50 to 74% of control)
HT High toxicity (MI < 50% of control)

TABLE 3.4.3.2
CHROMOSOMAL ABERRATIONS STUDY: EFFECTS ON MITOTIC INDEX (WITH METABOLIC ACTIVATION)

Test Substance (µg/ml)	Experiment 1				Experiment 2				Experiment 1			
	MI	% Δ	TOX	Eval	MI	% Δ	TOX	Eval	MI	% Δ	TOX	Eval
	Regular Harvest								Delayed Harvest			
-Control (DMSO)	64	-	NT	x	62	-	NT	x	51	-	NT	x
+Control (CP)												
28	82	+28	NT	x	66	+6	NT		54	+6		
42					62	-	NT	x	60	+18	NT	x
Telmisartan												
10	82	+28	NT	x	66	+6	NT	x				
50	74	+16	NT	x	66	+6	NT	x				
100					64	+3	NT		52	+2	LT	
125	38	-41	LT	x								
150					40	-35	LT	a	46	-10	NT	x
200					36	-42	LT	x	31	-39	HT	b
250	4	-94	HT									
500 (P)	1	-98	HT									

% Δ Percent change compared to DMSO Control
x 100 cells/culture scored
a < 100 cells/culture scored (toxic)
b < 50 cells/culture scored (toxic)

NT No toxicity (MI 75 to 100% of contol)
LT Low toxicity (MI 50 to 74% of control)
HT High toxicity (MI < 50% of controls)

The vehicle control cultures in the absence of the activation system had structural aberration frequencies (0-1.5%, excluding gaps) within the laboratory's historical control range (0-1.8%, mean = 0.22%). There was no increase in aberrant cell frequency at the regular and delayed harvests when cultures were treated with up to 100 µg/ml in the absence of metabolic activation. However, the number of aberrant cells increased to 5% (negative control 0%) ($P<0.05$) at the highest analyzable concentration of 125 µg/ml (Table 3.4.3.3). Besides breakage events, two chromatid-type exchanges (complex arrangements) were found. No conclusions could be drawn from cultures treated at concentrations of 200 or more µg/ml (no concentrations between 125 and 200 µg/ml used) since the number of cells available were limited due to cytotoxicity. In the repeat experiment, with blood from another donor, at a concentration of 150 µg/ml, the incidence of aberrant cells (2.3%) was not statistically significantly different from the concurrent control (0.5%), although a trend could be assumed. In contrast to the first experiment, no chromosomal rearrangements were found. At delayed harvest the aberration frequencies after telmisartan treatment (150 µg/ml) compared well with the control values. Adriamycin induced a clear increase in structural chromosome aberrations (8 to 34% excluding gaps) showing the sensitivity of the test system for the detection of clastogenic effects. Mainly chromatid breaks, fragments and exchanges were induced.

With the activation system, there was no increase in aberration frequency up to a concentration of 200 µg/ml (regular and delayed harvests). The percentage of aberrant cells excluding gaps was within the range of the concurrent (0 to 0.5%) and historical control data (0 to 2%) of the testing laboratory (Table 3.4.3.3). Singular gaps, fragments and breakages found in the first trial at

regular harvest were not confirmed in the 2nd trial at regular or delayed harvests. The positive control cyclophosphamide produced clastogenic effects of expected magnitude (4 to 12%). Additionally, chromosomal rearrangements were found.

TABLE 3.4.3.3
CHROMOSOME ABERRATIONS IN HUMAN BLOOD LYMPHOCYTES. DATA SHOWING PER CENT ABERRANT CELLS, EXCLUDING GAPS (% CA), AND POLYPLOID (% PP)

Concentration (µg/ml)	Culture	Exp. 1 72 hr		Exp. 2 72 hr		Exp. 3§ 72 hr		Exp. 2 96 hr (delayed)	
		% CA	% PP	% CA	% PP	% CA	% PP	% CA	% PP
Without Metabolic Activation									
-Control (DMSO)	A + B	0	2.0	0.5	0.5	0	1.0	1.5	0
+Control (ADR)									
0.05	A	34.0*	2.0			8.0*	2.0	28.0*	6.0
0.075	A			29.3*	0				
Telmisartan									
10	A + B	0	1.0	0	0	0	0		
50	A + B	0	0	0	0	toxic	0		
75	A					toxic	2.0		
100	A + B			1.0	0.5	toxic	5.1		
125	A + B	5.0¶	1.0			toxic	0		
150	A + B			2.3¶	0	toxic		0.5	1.0
200	A + B			toxic	0			toxic	1.5
250	A + B	toxic	3.0						
500P	A + B	toxic				toxic			
With Metabolic Activation									
Concentration (µg/ml)	Culture	Exp. 1 72 hr		Exp. 2 72 hr				Exp. 2 96 hr	
-Control (DMSO)	A + B	0.5	1.0	0.5	1.5			0	1.5
+ Control (CP)									
28	A	4.0*	1.0					28.0*	
42	A			12.0*	1.3			10.0¶	2.0
Telmisartan									
10	A + B	0.5	0.5	0.5	0				
50	A + B	0	0	1.0	1.0				
125	A + B	2.5	5.0						
150	A + B			0	2.2				
200	A + B			0.5	4.0			0.5	0.5
250	A + B	toxic							
500P	A + B	toxic							

A + B Blood from 2 different donors
P Precipitation
* Significantly different from vehicle control ($p \leq 0.05$)
§One culture only
¶ cytotoxic

Historical negative control values calculated on the basis of the most recent experiments (2306 metaphases): aberrant cells excluding gaps = 0.22% (range: 0-1.8%)

There were no consistent changes in the number of polyploid cells (predominantly 4 n and endomitosis) for the cultures treated with noncytotoxic concentrations of telmisartan, in the absence or presence of metabolic activation. Polyploidy rates, in the absence of cytotoxicity and metabolic activation, ranged from 0 to 1%. Polyploidy rates, in the presence of cytotoxicity but

in the presence of metabolic activation, ranged from 0 to 4%. The highest rate (5%) occurred in the presence of cytotoxicity, with or without metabolic activation (Table 3.4.3.3). According to the sponsor, though the values exceed the normal frequency rate for numerical aberrations (0-2%), the increases occurred in the presence of highly cytotoxic conditions and thus were not judged biologically meaningful.

In conclusion, telmisartan, in the absence of cytotoxicity, did not induce chromosomal aberrations in human peripheral lymphocytes *in vitro* (in the absence and presence of a metabolic activation system). However, at a concentration (125 µg/ml) which was clearly cytotoxic, producing >50% suppression of mitotic activity, a slight but statistically significant increase in aberration frequency was observed in the nonactivation system. The next higher concentration (150 µg/ml), which also was cytotoxic, induced an increase in aberrations which was not statistically significant. The response was not considered positive by the sponsor since the increase was not statistically significant at 2 or more concentrations with < 50% cytotoxicity. Furthermore, no clastogenic response could be documented in the metabolic activation system. Additionally, a tendency toward increased polyploidy rates was observed at cytotoxic concentrations both in the absence and presence of a metabolic activation system. Again, this was judged not biologically meaningful by the sponsor.

3.4.4. Micronucleus Assay (Report #U92-0334; Study #Gen Tox 05/92) Vol. 22

This GLP study was conducted by [redacted] between March 9 and April 8, 1992.

The micronucleus test is based on the principle that in anaphase, chemically-induced acentric chromatid and chromosome fragments lag behind and are not included in the daughter nuclei which are formed during telophase. Instead, these fragments, which are formed due to chromosome breakage or spindle disturbances, form micronuclei. Micronuclei are found in numerous cell types of bone marrow, but commonly the analysis is restricted to polychromatic erythrocytes (PCE). The purpose of the study was to investigate the potential of telmisartan to produce clastogenic (chromosome breaking) effects in mice.

Groups of 5 male and 5 female mice, 6-8 weeks old and weighing 23-32 g, were given telmisartan (batch #WE8110110) suspended in 0.5% hydroxyethylcellulose at single oral (gavage) doses of 0 (vehicle control), 250, 500 or 1000 mg/kg and sacrificed 24 hr later for bone marrow preparation. An additional group of 5 animals per sex was treated with the high dose and sacrificed 48 hr after dosing for bone marrow collection. A positive control group of 5 animals of each sex was given 30 mg/kg of cyclophosphamide orally by gavage and sacrificed at 24 hr post-dosing. Animals were observed for clinical signs of toxicity. Bone marrow was isolated from femoral bone and smears onto slides were prepared for evaluation. Frequency of micronucleated polychromatic erythrocytes (MN-PCE) was determined for each sample. As a measure of cytotoxicity, ratios of PCEs to normochromatic erythrocytes also were determined by counting 100 red cells per slide.

Results: No clinical signs of toxicity were observed. No significant increase in the number of PCEs containing micronuclei (0.06 to 0.3%) was observed after dosing up to 1000 mg telmisartan /kg compared with the corresponding negative control (0.14-0.10%). In contrast, animals treated with cyclophosphamide showed a significant increase in MN-PCE (1.66 to 1.70%). Thus, the sponsor concludes that telmisartan does not have clastogenic activity in mouse bone-marrow cells.

3.5. *Reproductive Toxicity Studies*

Definition of Indices

Birth index:	number of offspring born / number of implantation scars	X 100
Copulation index	number of animals successfully mated / number of animals paired for mating	X 100
Fertility index:	number of females pregnant / number successfully mated females	X 100
Gestation index:	number of females bearing live young / number of pregnant females	X 100
Viability index	number of live pups on day 4 / number of live pups on day 1	X 100
Weaning index	number of live pups on day 21 / number of live pups on day 4	X 100

3.5.1. Fertility and Early Embryonic Development Study in Rats (Report #U95-2031, Study #11S) Vol. 50

This GLP study, conducted by[ ]investigated the effect of telmisartan on gonadal function, estrous cycle, conception rate, fertility and early embryonic development through implantation. Dosing initiated on September 20 and October 4, 1993 for males and females, respectively.

Animals:[ ]rats; Males were approximately 53 days of age and weighed 229.8-266.4 gm, while females were approximately 74 day of age and weighed 194-243 gm, at initiation of dosing.

Mode of Administration/Dosage Levels: Suspensions of telmisartan (batch #8350071) were prepared in 0.5% Natrosol 250 HX (hydroxyethylcellulose). The drug was administered orally by gavage (10 ml/kg), once daily to three groups of 20 males and 20 females each at doses of 5, 15 or 100 mg/kg. Control animals (group 1) received the vehicle in a similar manner. Males were dosed for 28 days prior to cohabitation with treated females, with dosing continuing until occurrence of mating. The females were treated for 14 days prior to mating, during mating and until day 6 of gestation. Animals were housed individually in plastic cages. The doses were selected on the basis of a dose range-finding study in which doses of 50 and 200 mg telmisartan/kg/day, administered on gestation days 7 to 16, were associated with decreases in mean body weight gain, corpora lutea, implantations and viable fetuses.

Observations/Measurements: All animals were observed for physical signs twice daily (once on weekends). Body weights and food consumption were recorded weekly prior to mating and during pregnancy on days 1, 3, 6 and 14. For toxicokinetics study, blood samples were collected from the orbital sinus from satellite female animals (n = 4/dose group) under halothane anesthesia before treatment and 1, 3, 6 and 24 hr post treatment on gestation day 6. Females were killed on gestation day 14-16 under anesthesia and were examined for number of corpora lutea, number and position of implantation sites and early or late resorptions. After the mating period, the male animals were killed and the reproductive organs of those which had failed to produce a prgnancy were subjected to histological examination. It is not clear from the sponsor's text whether fetuses were examined grossly; however, from the tables it is clear that fetuses were discarded without further examination.

Results: There were no deaths in the study.

Males receiving 100 mg/kg/day showed a significant decrease ($p < 0.05$) in food consumption in weeks 3 and 4 of treatment. High dose females showed a decrease ($p < 0.05$) in food consumption only on gestation day 6. Mean body weight gain was statistically and dose-dependently decreased in mid and high dose group males during the entire treatment period (Table 3.5.1.1) (Fig 3.5.1.1). In females, a reduction in body weight gain was observed in all dose groups at the end of week 1 of pregnancy. The decrease in body weight gain in high dose group animals relative to control continued until necropsy (Table 3.5.1.1) (Fig 3.5.1.2).

TABLE 3.5.1.1
FERTILITY IN RATS: DIFFERENCES IN MEAN BODY WEIGHT (BW) AND BODY WEIGHT GAIN (BWG)

Males								
Dose (mg/kg/d)	Week 1		Week 2		Week 3		Week 4	
	Δ%		Δ%		Δ%		Δ%	
	BW	BWG	BW	BWG	BW	BWG	BW	BWG
5	-0.7	-7.1	-0.8	-4.1	-0.9	-3.9	-1.4	-4.7
15	-4.5*	-23.7*	-6.9*	-24.7	-7.4*	-22.0*	-8.4*	-22.1*
100	-5.1*	-30.8*	-9.0*	-35.2	-9.8*	-31.5*	-10.5*	-29.4*

Females										
Dose (mg/kg/d	Week 1		Week 2		GD 3		GD 6		GD 14	
	Δ%		Δ%		Δ%		Δ%		Δ%	
	BW	BWG	BW	BWG	BW	BWG	BW	BWG	BW	BWG
5	+0.4	+13.6	+0.1	+1.5	+0.5	-8.1	-1.0	-19.5*	-0.1	-2.1
15	-0.2	+15.2	+6.5*	+13.1	+0.3	-9.3	-1.4	-17.6*	-1.3	-8.4
100	+0.1	+13.6	-0.3	0.0	-0.9	-7.0	-2.6	-22.6*	-2.7	-10.1*

*: Statistically significant compared to controls ($p<0.05$) Week Week before mating
Δ%: Per cent difference from controls GD Gestation Day

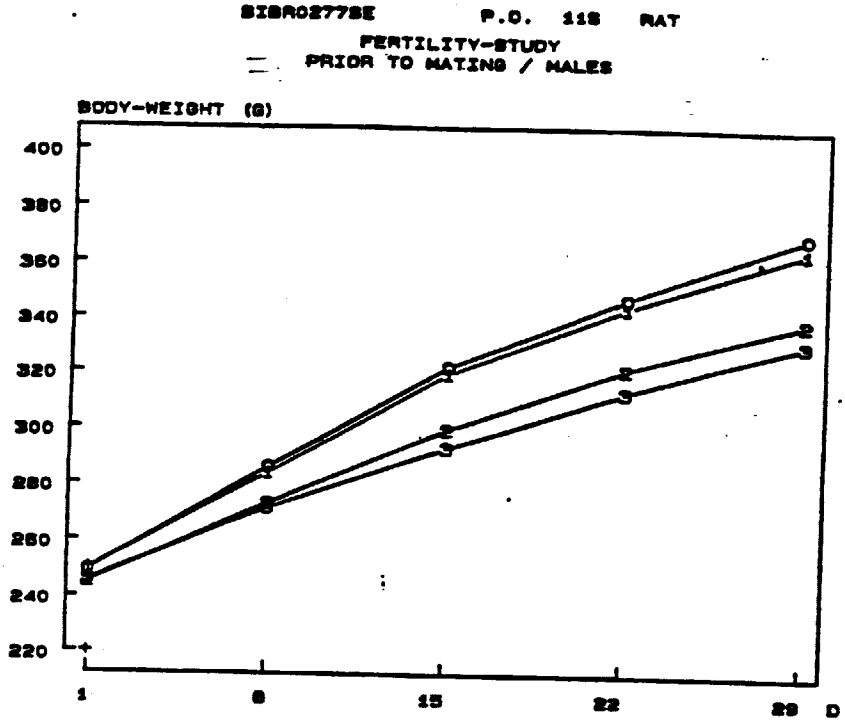


Fig. 3.5.1.1.: Mean body weights of male rats prior to mating. X axis: treatment in days, Y axis: weight in gm.
0: control
1: telmisartan 5 mg/kg/day
2: telmisartan 15 mg/kg/day
3: telmisartan 100 mg/kg/day

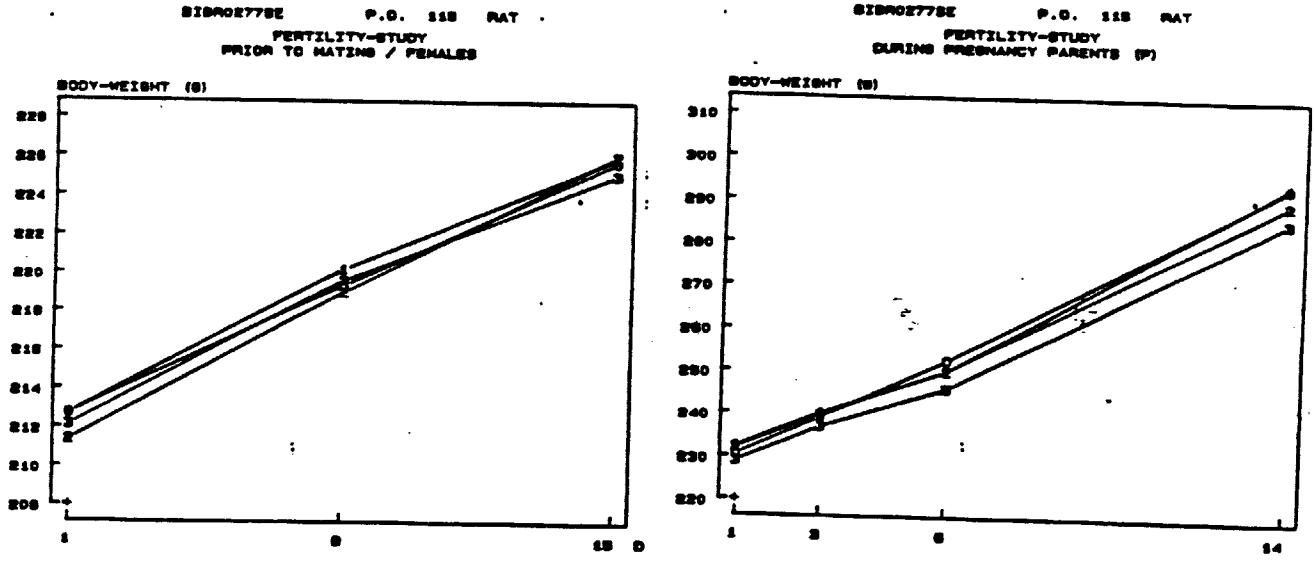


Fig. 3.5.1.2.: Mean body weights of female rats prior to mating (left side) and during pregnancy (right side). X axis: treatment in days, Y axis: weight in gm. 0: control, 1: telmisartan 5 mg/kg/day, 2: telmisartan 15 mg/kg/day
3: telmisartan 100 mg/kg/day .

Male fertility was unimpaired as shown by the normal copulation index. Fertility index was 70%, 90% and 90%, respectively, in dose groups 5, 15 and 100 mg/kg/day (control, 95%). No group differences were observed in the gestation index (100% in all groups including control). A decrease ($p < 0.05$) in the mean number of corpora lutea in females given 15 mg/kg/day and an increase ($p < 0.05$) in the number of late resorptions in animals given 5 mg/kg/day were noted (Table 3.5.1.2). The sponsor regards such deviations as biologically irrelevant since the numbers are within the historical control range. No dead fetuses were observed.

TABLE 3.5.1.2
FERTILITY STUDY IN RATS: MEAN NUMBER OF CORPORA LUTEA AND LATE RESORPTIONS

Parameter	Dose (mg/kg)				Historical Range [§]
	0	5	15	100	
Parental females F_0	20	20	20	20	
Females pregnant	19	14	17	18	
Total dead dams	0	0	0	0	
Resorptions only	0	0	0	0	
Corpora lutea, mean	15.7	14.8	14.2*	15.1	13.5 - 17.5
Implantations, mean	15	14.21	13.41	13.72	12.5 – 15.2
Viable fetuses, mean	13.53	12.29	12.41	12.22	
Dead fetuses	0	0	0	0	
Late resorption rate, % mean	0.05	0.21*	0.0	0.0	0 - 0.8
Total resorption rate, % mean	1.47	1.93	1.00	1.50	0.2 – 2.9
% Preimplantation loss	4.71	4.25	4.92	8.89	0 - 25.2

* Statistically significant compared to controls ($p<0.05$)
§ Calculated from vehicle controls and unaffected doses

There were no treatment-related necropsy findings in the males or females.

Mean plasma concentration of telmisartan measured in females on gestation day 6 increased with the dose and was nearly dose-proportional in the mid dose group but over proportional in the high dose group. High individual variability was present in all groups.

TABLE 3.5.1.2.
FERTILITY STUDY IN RATS: TOXICOKINETICS

Dose (mg/kg/d)	n	AUC_{0-24h} [µg·h/ml]		C_{max} [µg/ml]		Trough Level [µg/ml]
		mean	CV%	mean	CV%	
5	4	2.4	69.2	0.13	75.7	0.030
15	4	6.9	46.2	0.45	29.9	0.085
100	4	112.3	60.2	27.05	70.9	0.506

In summary, treatment-related reductions in body weight gain were noted in males and females at doses of 15 and 100 mg/kg/day. However, fertility and early embryonic development remained unimpaired at all dosage levels.

3.5.2. Developmental Toxicity Study in Rats (Report #U93-2079, Study #24R) Vol. 38-39

This GLP study, conducted by [redacted] investigated the effect of telmisartan during the period of organogenesis, parturition and development until weaning. Dosing initiated on June 9, 1992.

Animals: Female rats [redacted] were approximately 10 weeks of age and weighed 219.4-278.3 gm at initiation of dosing.

Mode of Administration/Dosage Levels: Suspensions of telmisartan (batch #8210040) were prepared in 0.5% hydroxyethylcellulose. The drug was administered orally by gavage (10 ml/kg), once daily to three groups of 36 mated females each at doses of 5, 15 or 50 mg/kg on gestational days 7 through 16. Control animals (group 1) received the vehicle in a similar manner. Animals were housed individually in plastic cages.

The doses were selected on the basis of a dose range-finding study in which doses of 50 and 200 mg telmisartan/kg/day were associated with decreases in mean body weight gain, corpora lutea, implantations and viable fetuses. A dose of 25 mg/kg/day did not produce toxic effects. No other information was provided (not even the days of administration) for the range-finding study.

Observations/Measurements: All animals were observed for physical signs twice daily (once on weekends) . Body weights were recorded on days 1, 7-16 and 21 of gestation. Food consumption was determined on gestation days 7, 14 and 21. For toxicokinetics study, blood samples were collected *via* the retrobulbar venous plexus from halothane anesthetized satellite animals (n=4) in the low and mid dose groups before treatment and 1, 3 and 6 hr post treatment on gestation day 16. Plasma levels of telmisartan were not measured in the high dose group in the current study as the sponsor had exposure data for this dose from a previous dose range-finding study.

On gestation day 22, 24 females were killed under pentobarbital anesthesia and were examined for number of corpora lutea, number and position of implantation sites and early or late resorptions. All fetuses were examined externally, weighed, sexed and classified as dead or alive. Approximately half of all fetuses from each litter were randomly selected, eviscerated and processed for skeletal examinations. The remaining fetuses were prepared for visceral examination. The remaining 12 dams per group were allowed to deliver their litters, rear their offspring for 3 weeks and were sacrificed on day 22 of lactation, and necropsied. The F_1 pups were counted, examined externally, and sexed on postnatal day 0. Body weights of the offspring were recorded on days 1, 4, 7, 14 and 21. The developmental parameters studied were incisor eruption (day 13), fur growth (day 16), auricular tract opening (day 16), eye opening (day 18) and correct running (day 18).

Results: There were no deaths or clinical signs observed in the study. On GD 16 body weight gain was transiently and largely dose-dependently decreased (10-16%) in all drug-treated groups ($P < 0.05$). However, on GD 21, a statistically significant decrease in body weight gain was observed only in the high dose group (Table 3.5.2.1). During the lactation period, body weight gain in the 50 mg/kg/day females was slightly higher than in the other groups, but absolute

weights remained slightly lower than those of controls (Fig 3.5.2.1). Food consumption was slightly but significantly ($p \leq 0.05$) decreased in all drug-treated groups in gestation weeks 2 and 3, with meaningful differences (~9.5%) in the 15 mg/kg group in GW 2 and the 50 mg/kg group in GW 3 (Table 3.5.2.1).

TABLE 3.5.2.1
DEVELOPMENTAL TOXICITY STUDY IN RATS: BODY WEIGHT AND FOOD CONSUMPTION

Dose (mg/kg)	N	Body Weight				Food Intake		N	Body Weight		
		GD 16		GD 21		GW	GW		LD 1	LD 21	
		BW Δ%	BWG Δ%	BW Δ%	BWG Δ%	2 Δ%	3 Δ%		BW Δ%	BW Δ%	BWG Δ%
0	31							11			
5	29	-3.4*	-10*	-2.8	-5.2	-4.5	-5.8*	10	-3.2	-2.6	+2.0
15	30	-4.5*	-13.8*	-3.1*	-5.8	-9.6*	-7.2*	12	-3.9	-3.7*	-2.8
50	33	-3.9*	-16.3*	-4.6*	-12.3*	-6.2*	-9.6*	10	-6.8*	-3.4	+18.8

* Significantly different from controls ($p<0.05$)
Δ% Percent difference from controls
BW Absolute body weight
BWG Body weight gain (%) from GD 1
GD Gestation Day
GW Gestation week
LD Lactation Day

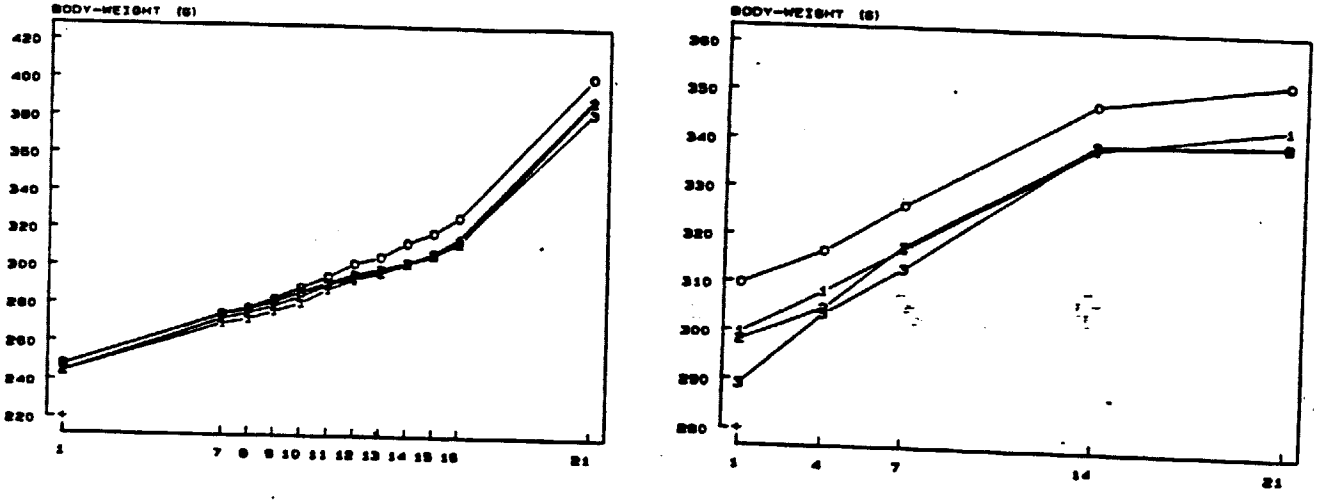


Fig. 3.5.2.1.: Average body weights of female rats (F_0) during pregnancy (left) and during lactation (right). X axis: treatment in days, Y axis: weight in gm. 0: control, 1: telmisartan 5 mg/kg/day, 2: telmisartan 15 mg/kg/day 3: telmisartan 50 mg/kg/day.

Pregnancy rate was comparable in all groups. No gross pathological findings were seen in the hysterectomy groups and no significant group differences in the mean number of corpora lutea, implantation sites, fetuses, early and late resorptions and mean fetal weight were noted. No dead fetuses were found. Sex ratio was within the normal range, except for a significantly higher ratio of female to male fetuses per litter at 5 mg/kg/day. This finding was considered incidental by the sponsor because of lack of dose dependency. Preimplantation loss and resorption rate were similar in all groups (Table 3.5.2.2).

TABLE 3.5.2.2
DEVELOPMENTAL TOXICITY STUDY IN RATS: LITTER PARAMETERS (HYSTERECTOMY GROUPS)

Dose (mg/kg)	Corp. lutea	Impl. sites	Viable Fetuses	Dead Fetuses	Sex Ratio (%)		Resorptions			Fetal Weight (g)	Preimpl Loss (%)	Resorp Rate (%)
					M	F	total	early	late			
0	16.35	15.15	14.35	0	55.51	44.49	0.8	.65	.15	5.38	7.26	5.17
5	16.42	16.37	15.37	0	47.18*	52.82*	1.0	.89	.11	5.21	0.35	6.02
15	16.89	16.00	15.00	0	56.64	43.36	1.0	.78	.22	5.28	5.21	6.37
50	16.22	15.30	14.61	0	53.42	46.58	0.7	.52	.17	5.23	5.65	4.34

*: Significantly different from controls ($p<0.05$)

Fetal weights were comparable in control and drug-treated groups. No skeletal or visceral malformations were observed. External examination of fetuses revealed no anomalies in the control and the treated groups. The incidence of single visceral and skeletal variations (delayed ossification of sternebrae and extremities, split sternebrae, lumbar and cervical ribs, dumbbell-shaped vertebrae, dilated cerebral ventricle and dilated renal pelvis) was similar among the groups. No malformations were observed in any of the treated groups.

There were no effects of test drug on any of the reproductive parameters in the natural delivery groups (Table 3.5.2.3). There were no treatment-related changes in mean litter size, pup sex ratio, survival (viability), gestation length or clinical signs at any dose level during the study. No drug-induced gross pathological changes were observed in dams.

TABLE 3.5.2.3
DEVELOPMENTAL TOXICITY STUDY IN RATS: LITTER PARAMETERS (LITTERING GROUPS)

Dose (mg/kg)	Implant.	Newborn Offspring	Postimpl. Loss (%)	Birth Index (%)	Sex (%)		Viable Rate (%)	Weaning Rate (%)	Wean. Rate Historical Range (%)
					M	F			
0	15.0	13.0	12.9	87.1	58.7	41.3	98.6	94.2	mean: 98.8
5	13.8	12.8	5.7	94.3	52.0	48.0	98.4	98.6	min.: 94.2
15	15.5	14.8	4.3*	95.7*	50.6	49.4	97.8	100.0	max.: 100
50	15.2	13.5	11.1	88.9	51.5	48.5	97.8	98.8	

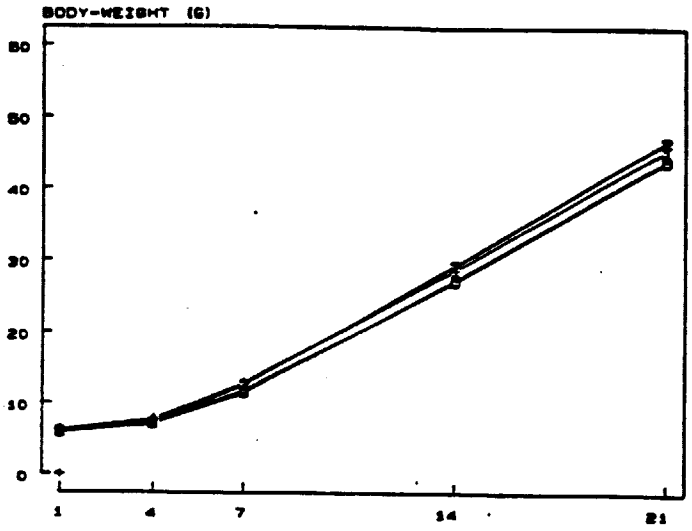
* Significantly different from controls ($p<0.05$)

Absolute body weight of F_1 offspring on day 1 was slightly, but significantly reduced (-6.2%) in the 50 mg/kg/day group relative to control, but body weight gain of F_1 pups during lactation was comparable (Table 3.5.2.4) (Fig. 3.5.2.2). The reduced birth weight was not considered biologically meaningful by the sponsor because mean fetal weight in the hysterectomy group was not significantly reduced.

TABLE 3.5.2.4
DEVELOPMENTAL TOXICITY STUDY IN RATS: F_1 PUPS BW AND BWG

Dose (mg/kg)	Birth Weight (g)	Body Weight (g) and Body Weight Gain (g)							
		LD 4		LD 7		LD 14		LD 21	
		BW	BWG	BW	BWG	BW	BWG	BW	BWG
0	6.10	7.28	1.18	11.77	5.67	27.04	20.94	43.85	37.75
5	6.12	7.70	1.58	12.85	6.73	28.74	22.62	45.55	39.43
15	5.85	7.30	1.44	12.50	6.65	29.34	23.48	46.73	40.88
50	5.72*	6.97	1.25	11.41	5.70	27.33	21.61	44.03	38.31

*: Significantly different from control ($p<0.05$), LD: Lactation Day



3.5.2.2.: Mean body weights of F_1 offspring. X axis: treatment in days, Y axis: weight in gm. 0: control, 1: telmisartan 5 mg/kg/day, 2: telmisartan 15 mg/kg/day 3: telmisartan 50 mg/kg/day.

There was no effect of treatment on the development of F_1 pups except for one pup in the high dose group with a 2-day delay in auditory canal opening. Gross examination detected no drug-induced changes, and no malformations or variations were observed.

Variabilities of AUC and Cmax were high in the 15 mg/kg/day dosage group. Time to reach peak concentration varied between 1 and 6 hr (median 3 hr). In all treatment groups pre dose concentrations (i.e. 24 hr trough levels on day 9 of Fig. .dosing, GD 15) of the parent compound were appreciable, demonstrating adequate 24 hr exposure to test substance.

TABLE 3.5.2.5
DEVELOPMENTAL TOXICITY STUDY IN RATS: TOXICOKINETICS

Dose (mg/kg)	AUC_{0-6h} [µg·h/ml]		C_{max} [µg/ml]		Trough Levels [µg/ml]
	Mean	CV (%)	Mean	CV (%)	Range
5	1.2	27.7	0.3	25.0	0.04 - 0.18
15	6.6	41.5	1.4	44.7	0.22 - 0.52
50*	24.1	43.0	7.0	61.8	0.35 - 0.75

*: data from dose range-finding study (U93-2115)

Conclusions: Treatment with telmisartan resulted in a slight, dose dependent decrease in body weight gain in maternal animals that did not affect reproduction capability or progeny. No teratogenic or embryotoxic potential was observed. The maternal NOEL was below 5 mg/kg/day. The NOEL for developmental toxicity was 50 mg/kg/day.

3.5.3. Prenatal and Postnatal Toxicity Study in Rats
(Report #U97-2107, Study #53S) Vol. 64-66

This GLP study, conducted by[redacted] investigated the effect of telmisartan on embryo-fetal development, parturition, lactation and neonatal growth, development and survival in rats. Dosing initiated on August 7, 1994.

Animals: Female rats[redacted] were approximately 10 weeks of age and weighed 206-259 gm at initiation of dosing.

Mode of Administration/Dosage Levels: Suspensions of telmisartan (batch #8350071) were prepared in 0.5% hydroxyethylcellulose. The drug was administered orally by gavage (10 ml/kg), once daily to three groups of 24 mated females each at doses of 5, 15 or 50 mg/kg from gestation day 6 to lactation day 21. Control animals (group 1) received the vehicle in a similar manner. Animals were housed individually in plastic cages.

Observations/Measurements: All animals were observed for physical signs twice (once on weekends) daily. Body weights were recorded on gestation days 1, 6-22, lactation day 1, 4, 7, 14 and 21. Food consumption was determined weekly during gestation and on lactation day 4, 7, 14 and 21. Plasma levels of telmisartan were not measured in this study. Duration of gestation, litter size, stillbirths and live births were recorded. Dams were necropsied on day 22 after delivery.

All F_1 pups were counted, examined for external abnormalities and sexed. Stillborn pups or those that died during rearing were examined for external and for visceral anomalies by necropsy. Histopathological examination was performed in tissues showing changes during necropsy. Pups were weighed on postpartum days 1, 4, 7, 14 and 21. Viability index (live pups on day 4/live pups on day 1 X 100) was determined on day 4 and each litter was reduced to 4 males and 4 females. Weaning index (live pups on day 21/live pups on day 4 X 100) was determined on day 21. Litters were culled to 2 males and 2 females after weaning. The pups were tested for maturational parameters (incisor eruption, fur growth, auricular tract opening, eye opening, correct running, testes descendent, vaginal opening) reflexes and sensory functions (pupillary reflex, air-righting reflex, hearing or preyer reflex) and behavior (maze and motility tests).

At about 10 weeks of age, F_1 animals (1 male and 1 female per litter) were mated within the same dose groups. Body weights were recorded on gestation days 1, 7 and 14. The pregnant F_1 dams were sacrificed on gestation days 14-16, and the number of corpora lutea, implants, live/dead fetuses and resorptions were counted. F_2 fetuses were not sexed and weighed, and were discarded without further examination. Reproduction and fertility parameters (copulation, fertility and gestation indices) were calculated. The testes of F_1 males whose corresponding females did not become pregnant were examined histopathologically.

Results: There were no mortalities. There were no test substance-related physical signs, deaths or abortions and no gross lesions observed at necropsies. A significant reduction in body weight gain from 9 through gestation day 22 was observed at 15 or more mg/kg/day . Additionally, starting on gestation day 12/13, a slight but progressive and statistically significant body weight

loss (maximum decrease 9%) was observed in dams of the 15 and 50 mg/kg/day groups. Absolute body weights of low dose animals were not significantly different from control, and reduction in body weight gain of this group was statistically significant (relative to control) only on GDs 11-13 and 15 (Table 3.5.3.1). Maternal body weight gain during lactation was comparable among the groups, though absolute body weights of high dose animals remained ~5.6% lower than control (Fig 3.5.3.1).

TABLE 3.5.3.1
PRENATAL/POSTNATAL STUDY IN RATS: MEAN BW AND BWG OF F_0 DAMS

Dose (mg/kg)	N	GD 7		GD 10		GD 15		GD 20		GD 22	
		BW	BWG	BW	BWG	BW	BWG	BW	BWG	BW	BWG
		Δ%	Δ%	Δ%	Δ%	Δ%	Δ%	Δ%	Δ%	Δ%	Δ%
5	19	-1.3	+6.6	-1.1	+2.7	-2.6	-10.4*	-2.6	-5.7	-2.9	-5.8
15	18	+0.3	+1.9	-0.6	-17.5	-4.3*	-31.8*	-7.9*	-27.7*	-9.2*	-27.0*
50	16	-1.0	+33.3	-2.8	-31.7*	-4.4	-22.8*	-8.1*	-24.5*	-8.8*	-22.8*

*: Significantly different from controls ($p<0.05$)
GD: Gestation Day
Δ%: % increase (+) or decrease (-) compared to controls

BW Absolute Body weight
BWG Body Weight gain (% from start)

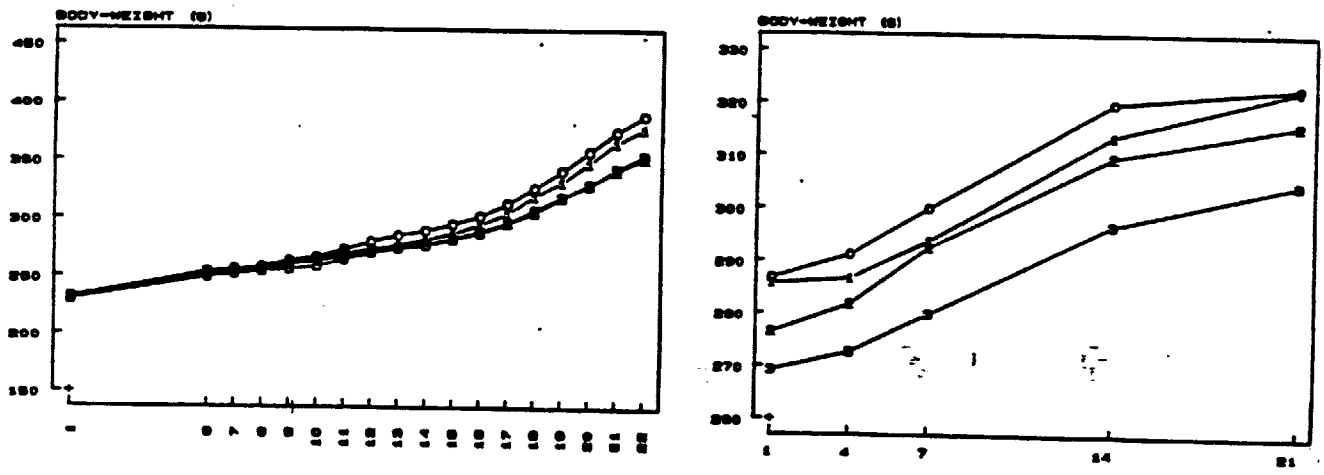


Fig. 3.5.3.1.: Average body weights of female rats (F_0) during pregnancy (left) and during lactation (right). X axis: treatment in days, Y axis: weight in gm. 0: control, 1: telmisartan 5 mg/kg/day, 2: telmisartan 15 mg/kg/day 3: telmisartan 50 mg/kg/day.

Food consumption was slightly, but significantly, lower than control in all drug-treated groups. Maximum differences of 12.4 and 14.0% were recorded for the 15 and 50 mg/kg/day groups, respectively, at the end of pregnancy (GD 21). The decrease was small in the 5 mg/kg/day group (maximum: 6.8% on GD 6). During lactation, food intake of the mid and high dose groups remained lower than control, and the decrease exceeded 10% for the high dose group.

TABLE 3.5.3.2
PRENATAL/POSTNATAL STUDY IN RATS: MEAN FOOD CONSUMPTIONOF F_0 DAMS

Dose (mg/kg)	GD 6		GD 21		LD 7		LD 14		LD 21	
	(g)	(Δ%)	(g)	(Δ%)	(g)	(Δ%)	(g)	(Δ%)	(g)	(Δ%)
0	100.6		184.5		121.0		384.1		467.4	
5	93.8*	-6.8	175.1*	-5.2	117.9	-2.6	384.2	+0.03	472.9	+1.1
15	93.0*	-7.6	161.6*	-12.4	113.1*	-6.5	369.2	-3.9	442.7*	-5.3
50	92.1*	-8.5	158.7*	-14.0	106.4*	-12.1	341.0*	-11.2	428.8*	-8.3

*: Significantly different from controls ($p<0.05$)
Δ%: Per cent difference from controls
GD Gestation Day
LD Lactation Day

Pregnancy rate was comparable in all groups. Gestation period was normal (22 days) in all control and drug-treated animals. No abortions or resorptions were noted; litter parameters were comparable in the control, 5 and 50 mg/kg/day groups. However, mean numbers of implantations and newborns were reduced, and postimplantation loss was increased at 15 mg/kg/day (Table 3.5.3.3). Since all of these values were near to or within the historical range for this rat strain and no dose-response was present, these deviations were judged incidental by the sponsor. On the other hand, viability rate (live pups on day 4/live pups on day 1 X 100) was decreased to 89.6% and 88.6% (controls 97.2%), respectively, at 15 and 50 mg/kg/day. But weaning rate (live pups on day 21/live pups on day 4 X 100) was unaffected in all groups (Table 3.5.3.3).

TABLE 3.5.3.3
PRENATAL/POSTNATAL STUDY IN RATS: LITTER PARAMETERS

Dose (mg/kg)	Impl. Sites (per litter)	Newborn Offspring (per litter)	Postimpl Loss (%)	Birth Index (%)	Sex Ratio (%) M	Sex Ratio (%) F	Viability Rate (%)	Weaning Rate (%)
0	15.2	14.1	7.1	92.9	54.5	45.5	97.2	100.0
5	14.6	13.9	4.5	95.5	52.0	48.0	97.7	100.0
15	12.9*	11.1*	14.8*	85.2*	49.1	50.9	89.4	100.0
50	13.6	13.2	4.0	96.0	45.4	54.6	88.6	100.0
HC m	14.3	12.8	12.2		55.0	45.0	98.5	99.3
r	13.5-15.0	12.8-12.9	10.0-14.0		51-58	42-49	98.5-99.0	98.4-100.0

*: Significant different from controls ($p<0.05$)
HC: Historical data in Chbb:THOM rats, m: mean, r: range

F_1 generation: No malformations or variations were observed in the control or any of the treated groups. There were no treatment-related clinical signs in the pups during lactation or after weaning. However, reductions in pup survival were observed in mid and high dose groups during postnatal days 1-4 (Table 3.5.3.4). No deaths occurred in the drug-treated groups after weaning.

TABLE 3.5.3.4
PRENATAL/POSTNATAL STUDY IN RATS: SUMMARY OF STATUS OF F_1 GENERATION PRIOR TO WEANING

Parameters	Control	5 mg/kg/day	15 mg/kg/day	50 mg/kg/day
Parental females F_0	24	24	24	24
Females pregnant	18	19	18	16
% Postimplantn. Survival (L.M.)	93.5[a]/92.9[b]	95.5/95.5	85.2/85.2	96.0/96.0
Females with live pups PND 1	18	19	18	16
Females with live pups PND 21	18	19	17	15
Total pups (females/males) PND 1				
live pups	114/140	130/135	100/99	118/93
dead pups	1/1	0	0	0
Live pups/ litter, L.M. (% live pups)	99.96	100	100	100
Pups dead before reduction (PND 4)	7	6	21	24
Live pups before reduction (PND 4)	247	259	178	187
Live pups after reduction (PND 4)	141	149	129	113
Pup deaths, L.M.				
postnatal days 0-3	2.56 (18 litters)	1.94 (19 litters)	9.85 (18 litters)	10.81 (16 litters)
postnatal days 4-7	0 (18 litters)	0 (19 litters)	0 (17 litters)	0 (15 litters)
postnatal days 8-14	0 (18 litters)	0.66 (19 litters)	0 (17 litters)	0 (15 litters)
postnatal days 15-21	0 (18 litters)	0 (19 litters)	0 (17 litters)	0 (15 litters)

LM = litter mean , PND = postnatal day
a: dead born pups included; b: dead born pups excluded (only intrauterine survival)

Statistically significant treatment-related reductions in absolute body weight (and body weight gain) of F_1 animals in the high dose group were observed at birth and throughout the lactation period (BW up to 12%; BWG up to 16%) (Fig 3.5.3.1) (Table 3.5.3.5). Post weaning body weight gain in F_1 rats of both sexes was similar in drug-treated and control groups. However, F_1 animals in the high dose group continued to show significantly lower than control body weight even after weaning.

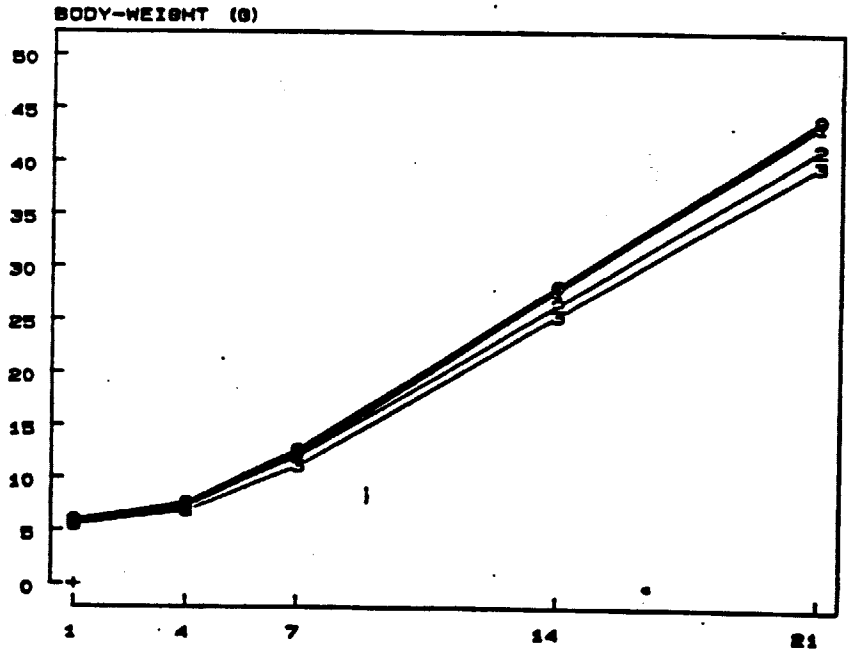


Fig. 3.5.3.1.: Average body weights of F_1 offspring during lactation. X axis: days, Y axis: weight in gm.
0: control, 1: telmisartan 5 mg/kg/day, 2: telmisartan 15 mg/kg/day, 3: telmisartan 50 mg/kg/day.

TABLE 3.5.3.5
PRENATAL/POSTNATAL STUDY IN RATS: MEAN F_1 BODY WEIGHT

Dose (mg/kg)	Mean Birth Weight		LD 4		LD 7		LD 14		LD 21	
			BW	BWG	BW	BWG	BW	BWG	BW	BWG
	(g)	(Δ%)	(Δ%)	(Δ%)	(Δ%)	(Δ%)	(Δ%)	(Δ%)	(Δ%)	(Δ%)
0	5.97									
5	5.81	-2.7	-4.1	-9.2	-3.6	-4.3	-1.3	-0.9	-1.2	-0.9
15	5.85	-2.0	-1.8	-1.2	-5.1	-7.8	-6.2	-7.4	-6.2	-6.8
50	5.49*	-8.0*	-9.5*	-16.0	-12.1*	-15.7*	-9.8*	-10.3*	-9.7*	-9.9*

* Significantly different from controls ($p<0.05$)
LD Lactation Day

Most developmental landmarks (i.e., fur growth, auditory canal opening, normal running, testes descent and vaginal opening) were comparable between groups. Incisor eruption was significantly delayed by one day in several offspring of all dose groups and by 2 days in one offspring in the 15 mg/kg/day group. According to the sponsor, the delays were not associated with significantly reduced F_1 body weight in the low and mid dose groups. Further the response lacked dose-dependency. Thus, the sponsor concludes that delayed incisor eruption was not judged clear evidence of maturational delay in drug-treated groups. Opening of the eyes was slightly but significantly delayed by one day in the high dose group (Table 3.5.3.6). This delay was considered drug-related and secondary to the reduced body weight gain.

TABLE 3.5.3.6
PRENATAL/POSTNATAL STUDY IN RATS: MATURATIONAL PARAMETERS

Dose (mg/kg/day)	Eruption of Incisors on Days			Opening of the Eyes		
	< 12	12 - 13	> 13	< 17	17 - 18	> 18
	%	%	%	%	%	%
0	100.0	0.0	0.0	98.6	1.4	0.0
5	87.8**	12.2	0.0	100.0	0.0	0.0
15	85.3**	14.0	0.8	95.3	4.7	0.0
50	86.7**	13.3	0.0	92.0*	8.0	0.0
Historical control	91.9			94.6		

* : Significantly different from controls ($p = 0.038$)
**: Significantly different from controls ($p<0.01$)

There was no effect of treatment on reflexes and sensory functions (pupillary and air-righting reflexes, hearing). One F_1 pup in the 5 mg/kg/day group showed no pupillary reflexes bilaterally and one in the 50 mg/kg/day group showed pupillary reflex unilaterally, but these isolated abnormalities were considered to be incidental by the sponsor since no morphological correlates were detected histopathologically. Behavioral tests revealed no meaningful group differences in the Biel water T-maze or motility tests (Actiframe). Except for a ventricular septal defect in one control offspring that died post-weaning, no variations or malformations were observed in stillborn or other pups that were examined for visceral anomalies. No drug-related gross pathological changes were observed.

Telmisartan had no adverse effects upon the reproductive capacity of the F_1 animals (Table 3.5.3.7). There were no abortions and no deaths. One F_1 female each of the control and 15 mg/kg/day groups was not pregnant. The reproductive tract of the non-pregnant 15 mg/kg/day F_1 female and the corresponding male did not show any histopathological changes. No microscopical examination was performed on the uterus of the non-pregnant control F_1 female as it was used for counting of implantation sites. The corresponding male had tubular atrophy of the testes and epididymal aspermia. No drug-induced effects on copulation or gestation indices were observed. The mean number of corpora lutea (15.9) was significantly decreased in the 50 mg/kg/day dose group. However, the values are within the historical data range for the strain used in this laboratory (Table 3.5.3.7). Mean numbers of implantations, viable fetuses, resorption rate and preimplantation loss compared well in all groups.

TABLE 3.5.3.7
PRENATAL/POSTNATAL STUDY IN RATS: MEAN LITTER PARAMETERS (F_1 GENERATION)

Dose (mg/kg)	Litters	Corp. lutea	Impl. sites	Viable Fetuses	Dead Fetuses	Resorptions			Preimpl. Loss (%)	Resorp Rate (%)
						total	early	late		
0	17	17.29	16.41	15.71	0	0.7	0.2	0.5	5.25	4.09
5	19	16.68	15.68	14.58	0	1.1	0.3	0.8	6.12	6.78
15	16	16.50	15.94	15.25	0	0.7	0.6	0.1	3.45	4.35
50	15	15.87*	15.00	14.20	0	0.8	0.7	0.1	5.37	4.94
HC	mean	15.2	14.3	13.5		0.8	0.8	0.1	5.9	5.7
	range	14.8-15.4	13.7-14.6	13.1-13.7		0.6-1.0	0.6-1.0	0	4.4-8.7	4.2-6.5

* Significantly different from control ($p<0.05$), HC: historical control data in Chbb:THOM rats

In summary, telmisartan administration was associated with reduced body weight gain and food consumption ($P < 0.05$) in F_0 pregnant rats at 15 and 50 mg/kg/day dose levels. The reduction was significant in low dose group animals only on certain occasions. No toxic effects were observed in F_1 offspring of 5 mg/kg/day dams. At 15 and 50 mg/kg/day, viability rate was reduced. In addition, a decrease in F_1 birth weight with slight maturational delay (opening of the eyes,) and body weight gain suppression during lactation was noted at the 15 and 50 mg/kg/day dose levels. Incisor eruption was significantly delayed by one day in several offspring in all dose groups. Fertility of the F_1 offspring was not impaired.

3.5.4. Developmental Toxicity Study in Rabbits (Report #U94-2119, Study #53S), Vol. 44

This GLP study, conducted by , investigated the effect of telmisartan during the period of organogenesis in rabbits. Dosing initiated on February 21, 1993.

Animals: Female rabbits were approximately 17-22 weeks of age and weighed 2092-2675 gm at initiation of dosing.

Mode of Administration/Dosage Levels: Suspensions of telmisartan (batch #8230231) were prepared in 0.5% hydroxyethylcellulose. The drug was administered orally by gavage (5 ml/kg), once daily to three groups of 16 pregnant females each at doses of 5, 15 or 45 mg/kg/day on gestation days 6 to 18. Control animals (group 1) received the vehicle in a similar manner. The doses were selected on the basis of a dose range-finding study in which rabbits were treated on gestation days 6 to 18. At the high dose level (40 mg/kg/day), a slight reduction in mean body weight gain (8% over the first 10 days of treatment, $p < 0.05$) was observed. There were no effects on reproduction or conceptuses. Animals were housed individually in stainless steel cages. Instead of water, saline solution was provided *ad libitum*.

Observations/Measurements: All animals were observed for physical signs twice daily (once on weekends). Body weights were recorded on gestation days 1, 6-18, 21 and 28. Food consumption was determined weekly. Plasma levels of telmisartan were not measured. Duration of gestation, litter size, stillbirths and live births were recorded. Dams were sacrificed on gestation day 29 and subjected to *in situ* examination. The following parameters were recorded: number of corpora lutea, number and position of implantation sites, live/dead fetuses, early and late resorptions, sex and fetal weight. All fetuses were given external, visceral and skeletal examinations. Type and incidence of fetal congenital variations and malformations were recorded.

Results: Transient diarrhea or mucoid stool was observed in all treated groups. Two high dose animals showed coprostasis (impaction of the feces in the intestine). One of these does exhibited weight loss (lost 65.2 gm or 2.8% of gestation day 1 weight) and died on gestation day 21. Though this animal did not exhibit gross pathological findings, the death was attributed to drug treatment.

In the high dose group, there was a treatment-related significant reduction in mean maternal body weight gain from GD 14 through GD 28 (Table 3.5.4.1). However, absolute body weights were not significantly different from those of control animals. Food consumption of high dose females was slightly (not significantly) lower than control on GDs 14, 21 and 28.

TABLE 3.5.4.1
DEVELOPMENTAL TOXICITY STUDY IN RABBITS: MEAN BODY WEIGHT GAIN

Dose (mg/kg)	N	GD 1 BW	GD 6 BW	GD 6 BWG	GD 9 BW	GD 9 BWG	GD 12 BW	GD 12 BWG	GD 18 BW	GD 18 BWG	GD 28 BW	GD 28 BWG
		Δ%	Δ%	g	Δ%	g	Δ%	g	Δ%	g	Δ%	g
0	12			14.3		-0.8		20.7		149.2		291.2
5	14	+1.3	+1.0	7.8	0.0	-29.2	+0.8	9.34	-0.6	104.8	+0.4	270.5
15	13	+0.2	+1.4	42.2	0.0	-6.8	-2.4	10.2	0.0	143.7	-0.3	293.7
45	10	+0.1	+0.7	27.5	-0.4	-13.5	-1.4	-15.6	-3.3	65.7*	-2.4	225.3*

* Significantly different from controls ($p < 0.05$)
GD Gestation Day
Δ% Percent difference from control value

No drug-related gross pathological changes were seen in dams. Due to 5/16 does with total resorptions, the gestation index was reduced (62.5%) in the 45 mg/kg/day group (control 100%). Except for the five high dose females showing an increase in postimplantation loss due to resorptions (resorption rate 18.19%) and corresponding decrease in number of viable fetuses, all pregnant females in all dose groups including control had viable fetuses (Table 3.5.4.2). Sex ratio of the 15 and 45 mg/kg/day groups showed a shift in favor of females. The significance of this shift was unclear. Mean live fetal weights were comparable among dose groups.

TABLE 3.5.4.2
DEVELOPMENTAL TOXICITY STUDY IN RABBITS: MEAN LITTER PARAMETERS

Dose (mg/kg)	FI %	GI %	CL	Impl. sites	Viable Fetuses	Dead Fetuses	Sex Ratio (%)		Resorptions			Fetal Wt (g)	PI Loss (%)	Resorp Rate (%)
							M	F	total	early	late			
0	75	100	7.5	7.1	6.7	0.8	56.4	43.6	0.3	0.3	0.0	35.90	4.43	4.70
5	87.5	100	8.0	7.4	6.5	0.0	51.6	48.4	0.8	0.4	0.4	36.96	8.24	11.01
15	81.3	100	7.8	7.1	6.0	0.0	38.5*	61.5*	1.1	0.9	0.2	37.75	9.30	15.51
45	100	62.5	7.4	6.7	5.6	0.0	38.3*	61.7*	1.1	0.4	0.7*	38.76	11.01	18.19*

* Significantly different from controls ($p<0.05$)
CL: Corpora lutea, FI: Fertility index, GI: Gestation index, PI: preimplantation loss

Gross, skeletal and visceral examination of the fetuses revealed three offspring with malformations: one in the control group with fused sternebrae, one in the 5 mg/kg/day group with cleft lip and palate and one in the 15 mg/kg/day group with a missing gall bladder. Additional findings without any dose-relationship were flexures, singular ventricular septal defects (VSD), missing, rudimentary and supernumerary ribs and synostosis of sternebrae. All these anomalies were classified by the sponsor as "variations due to their high frequency in this rabbit strain". However, as noted in Table 3.5.4.3, the historical control frequencies were all ≤ 1%.

TABLE 3.5.4.3
DEVELOPMENTAL TOXICITY STUDY IN RABBITS: FETAL EVALUATION

Findings	Doses (mg/kg)				Historical Data (%)
	0	5	15	45	
Runts	1	2	2	-	
(%)	(1.3)	(2.2)	(2.6)		1.0
Variations					
Flexures of limbs	2	-	1	-	
(%)	(2.5)		(1.3)		0.8
Ventricular septal defect (VSD)	2	4	2	-	
(%)	(2.5)	(4.4)	(2.6)		0.03
Lumbar ribs	-	2	-	-	
(%)		(2.2)			0.4
Missing ribs	1	-	-	-	
(%)	(1.3)				0.1
Short ribs	1	-	-	-	
(%)	(1.3)				‡
Malformations					
Cleft lip and cleft palate	-	1	-	-	
(%)		(1.1)			0.03
Missing gall bladder	-		1	-	
(%)			(1.3)		0.29
Fused sternebrae	1			-	
(%)	(1.3)				0.25

‡: No historical data available

Toxicokinetics: Plasma concentrations of telmisartan were measured in a dose-range finding study (report #98Q, study #U95-2109, conducted in February/March 1992) with doses similar to the main study except for the high dose.

Groups of 5 mated female rabbits ( ) weighing between 2.13 and 2.607 kg were used. Suspensions of telmisartan (batch #8110110) prepared in 0.5% hydroxyethylcellulose were administered orally by gavage (volume 5 ml/kg) once daily at doses of 5, 15 or 30 mg/kg/day on gestation days 6 to 18. Control animals received the vehicle in a similar manner. Blood samples were collected from the ear veins of 3 rabbits in each dose group on gestation day 13 at 0, 1, 2, 4 and 7 hr after dosing. The animals were sacrificed on gestation day 29. Animals did not receive saline supplementation.

Plasma concentrations of telmisartan showed high individual variability. Exposure (based on Cmax and AUC) was 2- to 7-fold higher than that achieved in the rat at comparable doses (see section 3.5.2). Except for 1/3 females in the 5 and 30 mg/kg groups, C_{max} and AUC_{0-7h} showed dose linearity with rising dose. Time to reach peak concentration (t_{max}) varied between 1 and 4 h (median: 1-2 h). Predose concentrations (i.e. trough levels) on gestation day 13 were appreciable at all doses indicating adequate exposure over a 24 h period.

TABLE 3.5.4.4
DRF DEVELOPMENTAL TOXICITY STUDY IN RABBITS: TOXICOKINETICS

Dose (mg/kg/d)	N	AUC_{0-7h} [µg·h/ml]		C_{max} [µg/ml]		N	Trough Level [µg/ml]
		Mean	CV (%)	Mean	CV (%)		Range
5	2	8.57	23.74	1.42	15.55	2	0.8 - 12.48
15	3	37.51	27.01	6.39	33.89	3	1.4 - 5.12
30	2	90.78	4.28	16.78	25.99	2	3.8 - 6.92

1/3 animals of the low (AUC: 146.6 µg·h/ml, Cmax: 22.3 µg/ml) and high (AUC: 237.2 µg·h/ml, Cmax: 46.9 µg/ml) dose groups with exceptionally high values excluded from the mean.

In summary, with saline supplementation, significant maternal toxicity resulting in one death, reduced body weight gain, marginally reduced food consumption and total resorptions in 5/16 does, were observed in the 45 mg/kg/day group. It cannot be said with certainty whether the early embryonic deaths were secondary to maternal toxicity or a direct embryotoxic effect of telmisartan. However, increased late resorptions can be due to direct embryotoxicity, and resorption of entire litters is usually a consequence of maternal toxicity. Telmisartan showed no teratogenic potential. Malformations and variations were nonspecific and similar in vehicle and drug-treated groups, were observed at low frequency and did not increase with dose. Based on these results, the maternal and embryonic NOAEL was 15 mg/kg/day. From the dose range-finding study toxicokinetics data, it appears that 15 mg/kg/day provides a Cmax 6-fold higher, and an AUC at least 16-fold higher, than the C_{max} and AUC for female human volunteers receiving 120 mg/day (1.06 µg/ml and 2.38 µg.h/ml, respectively), a dose 50% higher than the MRHD of telmisartan. (Note that $AUC_{0-7\,hr}$ in rabbit is compared with AUC_{0-24hr} in human.)

3.5.5. Placental Transfer of ^{14}C-Telmisartan in Rats
(Report #U96-0197, Study #NBIBC-9622) Vol. 51

This non-GLP study, conducted by

investigated the placental transfer of radioactivity after oral administration of ^{14}C-telmisartan to pregnant rats. Study conducted in 1995 (exact dates not provided).

Animals: 12th and 18th day pregnant rats (Sprague-Dawley) were approximately 12-13 weeks of age and weighed 212-306 gm, and 259-309 gm, respectively at initiation of dosing.

Mode of Administration/Dosage Levels: Solutions of ^{14}C-telmisartan (batch #Br 872/26) were prepared in ethanol, sodium hydroxide and water. The drug was administered to non-fasted rats orally (stomach tube) as a single dose of 1 mg/kg on day 12 or 18 of pregnancy.

Observations/Measurements: For 12th day pregnant rats, blood was taken from the abdominal aorta under anesthesia 4, 8, 24, 48 and 96 hr after administration of ^{14}C-telmisartan. At the same times maternal tissues (liver, kidney, lung and heart) and two samples each of the placenta, fetus, and amniotic fluid were collected from each dam (n=3 per sample time). For 18th day pregnant rats, maternal blood and tissues (liver, kidney, lung and heart) were taken 4, 24 and 48 hr after administration of ^{14}C-telmisartan (n=3 per sample time). Additionally, four samples each of the placenta, fetus, and amniotic fluid were collected from each dam, and the liver, kidney, lung and heart were taken from the two of the four fetuses.

Results: The concentration of radioactivity in maternal blood, plasma and selected tissues was highest 4 hr after administration, and decreased with time in rats dosed on day 12 of gestation. In the same animals, the radioactivity found in the placenta and fetus showed maximum values at 8 and 4 hr, respectively. The amniotic fluid showed the maximum value at 24 hr (Table 3.5.5.1). Concentrations were below the level of detection 96 hr post dose.

The pattern of distribution of radioactivity in 18th day pregnant rats was similar to that for the 12th day pregnant rats except for the higher levels of radioactivity in maternal blood and plasma at all time points investigated. The concentration of radioactivity in the placenta of the 18th day pregnant rat was about 1/3 of that in the maternal blood, then decreased with time. The concentration in the amniotic fluid increased with time and peaked at 48 hr, surpassing the maternal blood level. Distinct concentrations of radioactivity were found in whole fetus, fetal liver, fetal kidney and fetal lung. All these showed highest levels 24 hr after administration, exceeding the maternal blood levels at that time (Table 3.5.5.2). The radioactivity is transferred into the fetus as free drug. The free fraction of drugs with high protein binding (>99%) seems to increase in the prenatal period. At the same time the concentration of albumin and α_1-acid glycoprotein in maternal serum decreases as gestation progresses.

TABLE 3.5.5.1

PLACENTAL TRANSFER OF RADIOACTIVITY AFTER ORAL ADMINISTRATION OF 1 MG/KG [^{14}C] TELMISARTAN TO 12TH-DAY PREGNANT RATS

Tissue	n	Concentration [ng-eq telmisartan/g or ml] 4 hr	8 hr	24 hr	48 hr	96 hr
Liver	3	3149.42 ± 1063.99	2779.15 ± 559.59	310.56 ± 94.60	134.57 ± 125.70	0.00
Kidney	3	46.00 ± 15.96	43.11 ± 17.14	12.02 ± 1.33	3.60 ± 3.63	0.00
Lung	3	22.89 ± 7.57	21.81± 8.37	5.81± 1.20	1.76± 3.05	0.00
Heart	3	13.44 ± 6.50	11.42 ± 5.38	1.16 ± 2.00	0.00	0.00
Whole blood	3	27.79 ± 12.49	26.78 ± 13.50	4.12 ± 0.83	2.49 ± 2.89	0.00
Plasma	3	43.56 ± 18.73	34.47 ± 14.71	5.98 ± 0.98	3.65 ± 3.93	0.00
Placenta	12	12.03 ± 10.57	14.37 ± 9.27	1.86 ± 2.94	0.46 ± 1.11	0.00
Amniotic fluid	12	0.00	4.09 ± 6.44	5.33 ± 4.24	2.73 ± 3.18	0.00
Fetus	12	11.83 ± 8.02	11.03 ± 6.83	7.98 ± 1.72	1.89 ± 2.93	0.00

Each value represents the mean ± SD

TABLE 3.5.5.2

PLACENTAL TRANSFER OF RADIOACTIVITY AFTER ORAL ADMINISTRATION OF 1 MG/KG [^{14}C] TELMISARTAN TO 18TH-DAY PREGNANT RATS

Tissue	n	Concentration [ng-eq telmisartan/g or ml] 4 hr	24 hr	48 hr
Liver	3	3321.09±206.15	621.65±139.85	274.79±325.33
Kidney	3	57.30±4.17	18.59±3.44	9.23±7.12
Lung	3	33.40±4.28	9.60±1.01	5.44±5.12
Heart	3	18.96 ±3.83	2.93±2.54	2.69±2.34
Whole blood	3	59.63±9.09	13.99±2.36	6.21±6.50
Plasma	3	77.05±12.10	19.73±3.66	9.01±8.99
Placenta	12	22.29±1.93	13.07±1.01	8.55±3.16
Amniotic fluid	12	0.92±0.98	13.41±2.09	16.18±5.38
Fetus	12	13.72±2.25	45.27±6.58	17.65±3.80
Fetal liver	6	14.07±1.95	23.80±3.58	12.83±2.58
Fetal kidney	6	14.27±16.06	29.01±16.47	14.49±6.85
Fetal lung	6	18.73±4.10	25.49±1.81	9.72±1.69
Fetal heart	6	11.13±17.25	17.18±18.83	20.44±12.16

Each value represents the mean ± SD

3.5.6. Transfer of ^{14}C-Telmisartan into Milk in Rats
(Report #U96-0196, Study #NBIBC-9621) Vol. 51

This non-GLP study, conducted by

investigated the excretion of radioactivity into milk after oral administration of ^{14}C-telmisartan to lactating rats. Study conducted in 1996 (exact dates not provided).

Animals: Lactating rats (Sprague-Dawley) were approximately 15 weeks of age and weighed 250-300 gm at time of dosing.

Mode of Administration/Dosage Levels: Solutions of ^{14}C-telmisartan (batch #Br 872/26) were prepared in ethanol, sodium hydroxide and water. The drug was administered to non-fasting rats orally (stomach tube) as a single dose of 1 mg/kg on lactation day 12/13.

Observations/Measurements: Blood (from the retro-orbital plexus under anesthesia) and milk were collected from 4 to 5 animals 0.5, 2, 4, 8, 24, 48 and 72 hr after administration of radioactivity. The pups were separated from the dams 30 min before each milking. Oxytocin (1 IU/ml/kg) was given i.p. to increase the milk production. The dams were housed with pups again after milking. Radioactivity in samples was measured by liquid scintillation counting.

Results: After oral administration of 1 mg/kg ^{14}C-telmisartan, the radioactive material(s) appeared in the systemic circulation and milk in the first sampling period, 30 min post dose. In the plasma, maximum mean ^{14}C concentration was observed between 4 and 8 hr and declined thereafter. In the milk, the maximum mean ^{14}C concentration was observed at 8 hr post dose. The concentration of radioactivity in the milk was about 1.5 to 2 times higher than in the plasma. The radioactivity was not quantifiable in both plasma and milk 72 hr after administration (Table 3.5.6.1).

TABLE 3.5.6.1
CONCENTRATIONS OF RADIOACTIVITY IN PLASMA AND MILK OF LACTATING RATS AFTER ORAL ADMINISTRATION OF ^{14}C-TELMISARTAN

Time (hr)	Concentration (ng Eq. telmisartan/ml) (N=5)	
	Milk	Plasma
0.5	3.32 ± 6.65 (n=4)	23.77 ± 5.30
2	30.60 ± 4.78 (n=4)	31.04 ± 7.65
4	54.24 ± 17.51	34.84 ± 7.01
8	66.08 ± 26.21	36.12 ± 11.89
24	13.52 ± 10.19	9.30 ± 4.33
48	6.79 ± 7.25	4.06 ± 4.17
72	0.00	0.00

Each value represents the mean ± SD

4. OVERALL SUMMARY AND EVALUATION

Pharmacodynamics

Telmisartan is a non-peptidic, orally-effective, potent and specific antagonist of angiotensin II, active at the AT_1 receptor. It was developed by Boehringer Ingelheim Pharmaceuticals, Inc., for the treatment of essential hypertension.

The mechanism of the interaction between telmisartan and the AT_1 receptor is complex: the antagonism was characterized as competitive antagonism in rat lung receptor binding studies, non-competitive unsurmountable antagonism in isolated rabbit aorta, and noncompetitive antagonism in decreasing blood pressure responses to angiotensin II in pithed rat preparations. The activity of telmisartan is highly selective: the compound is inactive in binding studies with many other neurotransmitter receptors.

Telmisartan *per se* at a dose of 30 mg/kg p.o. reduced diastolic blood pressure significantly in normotensive rats, rabbits and dogs. In angiotensin II-induced hypertension in rats, both i.v. (0.1, 0.3 or 1 mg/kg) and oral (0.3 or 1 mg/kg) administration of telmisartan caused dose-dependent decreases in b.p. and the inhibitory effect was long-lasting (> 5 hr). Dogs seem to be more sensitive with 0.01 and 0.03 mg/kg i.v. reducing the pressor response to angiotensin II significantly for more than 7 hr. Similarly, oral administration of telmisartan (0.03, 0.1 and 0.3 mg/kg) decreased the angiotensin II-induced pressor response in a dose-dependent manner and the effect observed at the dose of 0.3 mg/kg lasted beyond 28 hr. This long lasting effect could result from the slow dissociation or slow off-rate of telmisartan from its binding sites. In conscious, sodium-depleted normotensive Cynomolgus monkeys, both oral and i.v. routes of administration (0.3 to 10 mg/kg) caused dose-dependent significant decreases (up to 42%) in mean arterial pressure without any significant effect on the heart rate. The effects were observed within 1 hr with the maximum effect reached within 2 hr, remaining unchanged up to 7 hr postdose. The hypotensive effect of 0.3 or more mg/kg at 24 hr was modest (11%), but statistically significant. The test substance also caused dose- and time-dependent increases in plasma renin activity (PRA) and plasma levels of angiotensin II. Similarly, in marmosets, telmisartan (0.3 mg/kg i.v.) effectively inhibited the angiotensin II-induced pressor response in a time-dependent manner.

In 2 kidney, 1 clip renal hypertensive rats (RHR), telmisartan at 0.3 and 1 mg/kg, p.o. b.i.d. induced a marked and sustained (>24 hr) hypotensive effect . The reductions in mean blood pressure after 4 days of dosing at 0.3 and 1 mg/kg, p.o. were 37 and 68 mm Hg, respectively. In spontaneously hypertensive rats (SHR) receiving these same doses over the same time period, but only once a day, reductions in mean blood pressure were 23 and 22 mmHg, respectively. This suggests that plasma renin activity is nearly normal or unchanged in SHR and thus angiotensin II receptor antagonists such as telmisartan that interact with the renin angiotensin system, are less effective in the SHR model than in a model with high plasma renin activity. There were no significant changes in the heart rate in either hypertension model.

In renal function studies, telmisartan was shown to increase urine production and sodium excretion at 0.1 and 0.3 mg/kg but lacked any effect at 1 mg/kg, p.o. The lack of effect at 1

mg/kg could be due to selective dilation of the efferent arterioles, which could result in a drop in renal perfusion pressure, effective filtration pressure and GFR. Oral administration of telmisartan to normotensive rats in dosages of 50 mg/kg/day for 2 weeks resulted in a significant increase in the plasma levels of BUN and creatinine. However, salt administration during the dosing period completely prevented the drug-associated increase in BUN and creatinine. It was concluded that a positive sodium balance leads to a down-regulation of the renin angiotensin system in these animals and prevents the renal effects of angiotensin II receptor blockade after administration of a high dose of telmisartan. In isolated rat kidney studies, telmisartan (cumulative concentrations of 10, 100 and 1000 nM) resulted in concentration-dependent and significant increases in urinary flow, renal perfusate flow, and GFR. A possible mechanism of this action is inhibition of the vasoconstrictive effect of intrarenally generated angiotensin II on afferent and efferent arterioles. *In vivo* studies in both rats (0.1 to 1 mg/kg i.v.) and dogs (0.03 to 0.3 mg/kg i.v.) have shown telmisartan to increase excretion of water, Na^+ and chloride (at all dose levels) with no effect on potassium excretion. Thus, telmisartan has diuretic and natriuretic effects in both dogs and rats.

In other pharmacology studies, telmisartan (up to 30 mg/kg p.o.) had no marked activity in tests designed to assess potential activity on the CNS in rats and mice. Further, telmisartan did not potentiate hexobarbital-induced sleeping time in rats and bradykinin-induced bronchoconstriction in guinea pigs. Additionally, telmisartan 1-*O*-acylglucuronide, the main metabolite of telmisartan is devoid of hemodynamic effects and any angiotensin II antagonistic effect in anaesthetized rats at doses equivalent to and three-fold higher than those of the active compound, telmisartan.

Drug Disposition (ADME)

Absorption and Pharmacokinetics

Telmisartan was rapidly absorbed after oral administration (t_{max} 1 - 2 h) in mice, rats and dogs and slowly in rabbits (7 hr). Absorption after oral administration was high (>60%) in mice and rats, yielding an absolute bioavailability between 56% and 75%, but low (<20 %) in dogs. Absorption and/or bioavailability in dogs was influenced by food. High interindividual variability was observed in both the fed and the fasted state. Nevertheless, trends towards higher C_{max} (+37 %) and higher AUC values (+30 %) were observed in fed as compared to fasted dogs (see Table in section 2.1.8). Similar studies were not conducted in other species. In mice and humans, C_{max} and AUC were higher in females than in males. A similar gender effect was not clearly demonstrated in rats and dogs (see Table in section 2.1.9).

Maximum plasma concentration after oral administration of 1 mg/kg was comparable in rats, dogs and humans (43 - 61 ng/ml) and higher in mice (183 - 240 ng/ml) and rabbits (158-242 ng/ml). The half-life of elimination ($t_{½}$) after oral administration was approximately 7 to 10 hours in mice, rats and dogs and >14 hours in rabbits and humans. After intravenous administration, $t_{½}$ was approximately 2-fold longer in dogs only. In mice, rats and dogs it was shown that the concentration time profile of the parent compound was comparable to that of the radioactivity. This indicated that the radioactivity in plasma represented predominantly the parent compound. In the rabbit, the ratio of parent compound to radioactivity was approximately 0.5 and thus equal amounts of metabolites and of the parent compound were present in plasma, indicating comparable pharmacokinetics of the parent compound and of the metabolite(s).

In rats and dogs, telmisartan exhibited dose proportional pharmacokinetic profiles with single rising oral doses up to 10 mg/kg in the rat and 30 mg/kg in the dog. However, higher doses in these species resulted in a positive deviation from dose proportionality for AUC and C_{max}. Similar non-proportionality is also seen in humans (see below for explanation). Trough levels (predose concentration) were high at all doses in rabbits indicating constantly high exposure to test substance.

Distribution

Telmisartan administered orally to rats was found to concentrate predominantly in the plasma fraction of the blood. Only 6 - 11 % of the radioactivity distributed into the red blood cells during the time period of 0.5 - 24 hours. The limited partitioning of telmisartan and its metabolite into red blood cells of rats might be due to binding to plasma proteins, which was very high in all species examined (98.7-99.6%). The free fraction of telmisartan in dog plasma (1.3%) was three times higher than the free fraction of telmisartan in human and rat plasma (0.4%). These high levels of plasma protein binding can lead to adverse drug reactions when telmisartan is administered in the presence of other highly protein-bound compounds. Further, the higher binding to protein results in slower metabolism of the parent compound in both animals and humans. No such studies were conducted in rabbits.

Telmisartan was quickly distributed into a volume larger than total body water (V_{ss} rats = 5.3 L/kg, V_{ss} dogs = 1.7 - 3.0 L/kg). Rat autoradiography and quantitative distribution studies found the highest concentration of radioactivity in the liver. Lower concentrations were found in blood, lung, renal cortex and myocardium. Radioactivity in the central nervous system (CNS) was below the photographic detection limit and could only be measured by quantitative distribution study. After eight hours, most of the tissues were free of radioactivity, except the liver and the gastrointestinal tract. In pregnant rats, telmisartan and/or its metabolites increasingly crossed the placenta with increasing time of gestation. Radioactivity was found in the rat whole fetus, fetal liver, fetal kidney and fetal lung. All showed highest levels 24 hr after administration, exceeding the maternal blood levels at that time. The radioactivity was transferred into the fetus as free drug and its elimination from the fetus was slow.

Metabolism

Telmisartan circulated preferentially (80 - 90 %) as parent compound in the plasma of most species investigated, including humans. The *in vitro* metabolism was investigated in microsomes from rat liver, kidney, small intestine and lung, and in hepatocytes from rat and human liver. It was shown that telmisartan was readily glucuronidated in microsome preparations of rat liver, kidney and small intestine; however, glucuronide was not formed in lung microsomes. The affinity of telmisartan for the liver enzyme was higher than its affinity for the enzymes from the small intestine and kidneys. Studies with isolated perfused rat livers demonstrated that the rate of metabolism of parent compound in the liver was slow but that the elimination of telmisartan glucuronide was fast. In addition it was found that the liver had a large but limited capacity to retain the drug. The non-proportional increase in telmisartan plasma concentrations at higher doses is probably caused by a saturable metabolism in the gut (due to a limited storage of uridine 5' diphosphoglucuronic acid cofactor) and a saturable uptake by the liver. In human hepatocyte culture studies, the primary metabolite identified also was the acylglucuronide of the parent compound. Chromatographic, enzymatic and mass spectrometric methods showed that this

metabolite was identical to the metabolite isolated from rat bile. The detection of the acylglucuronide in human hepatocytes was important, since >98 % of the radioactivity dosed intravenously to humans appeared in the feces as unchanged drug. Less than 1 % of the dose was excreted in urine as glucuronide. *In vivo* studies with rat bile have confirmed that telmisartan was primarily metabolized by a phase II reaction (glucuronidation). The metabolite was determined to be the acylglucuronide of the parent drug. In mice, the main biliary metabolite was the 1-*O*-acylglucuronide, which contributed 50 - 80% of total radioactivity. The metabolism of telmisartan in animals was similar in all species investigated (mouse, rat, dog), although in mice, an additional radioactive metabolite, accounting for 5 - 11% of total radioactivity, was identified in bile. This product was identified as a glycoside of the parent compound (telmisartan conjugated to a hexose sugar). The latter metabolite was not observed in any other species studied, including humans. No metabolism studies were done in rabbits.

Pharmacokinetics of the telmisartan 1-*O*-acylglucuronide was assessed after intravenous administration in rats. The metabolite was more quickly eliminated ($t_{1/2}$ ~10 minutes) than the parent compound. Telmisartan 1-*O*-acylglucuronide was not hydrolyzed to the parent compound *in vivo*. The acylglucuronide did not inhibit the angiotensin II pressor response in anesthetized rats; hence it is not pharmacologically active. The data obtained in an enzyme induction study in rats did not demonstrate any evidence for the induction of cytochrome P-450 dependent enzyme activity by oral administration of 25 mg/kg/day telmisartan for three consecutive days.

Excretion

The administered dose of telmisartan was preferentially eliminated in the feces via biliary secretion in all animal species and humans. Only very small amounts (<1%) of the dose were eliminated renally, most probably due to the high molecular weight of telmisartan. Autoradiographic pictures of the upper gut after administration of an intravenous dose in rats demonstrated that the radioactivity was quickly eliminated via biliary excretion. Quantitative studies in isolated perfused rat liver showed that once the acylglucuronide was formed from telmisartan it was almost instantaneously eliminated via bile. Therefore the acylglucuronide metabolite did not interfere with the elimination of the parent compound. The enterohepatic recycling in rats was rather low, about 10%, mainly due to glucuronide conjugate recycling; no parent drug was involved in the process.

Lactating rats dosed with ^{14}C telmisartan readily excreted telmisartan and/or its metabolite into milk, and the concentration of the radioactivity in milk was approximately twice its concentration in plasma.

Toxicology

Acute Toxicity

Single dose toxicity studies were performed with telmisartan in rats and dogs by the oral (2000 mg/kg) and intravenous (150 to 300 mg/kg in rats only) routes of administration. Oral administration did not cause deaths or signs of toxicity in either species. On the other hand, iv administration was moderately toxic to rats. At doses of 150 or more mg/kg, marked clinical signs of toxicity appeared immediately after dosing, and included salivation, sedation, prone or lateral position, ptosis, hypopnea and cyanosis. Peripheral vasodilation and tonic-clonic

convulsions were noted at doses of 200 or more mg/kg. All animals receiving 300 mg/kg died within 40 min of administration, while 2 of 6 given 200 mg/kg and all animals given 250 mg/kg died within 24 hr of dosing. The macroscopic examination of dead animals showed pulmonary edema, congestion of multiple organs, petechia of the thymus and hemorrhagic erosions of the stomach. Deaths were attributed to circulatory collapse due to exaggerated hypotensive activity of the test substance.

Chronic Toxicity

The potential for adverse effects following repeated administration of telmisartan was investigated in the rat and the dog. The duration of the oral studies in the rat and the dog ranged from 4 weeks to 12 months in rats (24 months when carcinogenicity studies are considered) and from 4 weeks to 12 months in dogs. The duration of intravenous administration was four weeks in both species. Additionally, the carcinogenic potential of telmisartan was evaluated in a 24 month study in mice.

Rats:

The chronic toxicity of telmisartan was evaluated in rats at oral (gavage) doses of up to 500 mg/kg/day for 26 weeks and up to 100 mg/kg/day for 104 weeks (dietary administration), and at intravenous doses of up to 20 mg/kg/day for 4 weeks. 500 mg/kg/day was lethal to 9/20 animals and gastrointestinal injury was considered the cause of death. Dose-dependent decreases in body weight gain and food consumption were observed for males at doses as low as 4 mg/kg/day when administered by gavage, 15 mg/kg/day when administered in the diet, and 20 mg/kg/day i.v. In females, significant decreases in body weight gain and food consumption were observed only at much higher doses (500 mg/kg/day for 13 weeks). Notable findings at doses as low as 50 mg/kg/day p.o. and 20 mg/kg/day i.v. (as early as 1 month) were mild to moderate anemia, decrease in thromboplastin time, increases in BUN, creatinine and cholesterol. Bilirubin levels were increased (>90% over control) in rats receiving 100 mg/kg/day for 104 weeks or 500 mg/kg/day for 13 weeks. Treatment-related reductions were recorded for absolute and/or relative heart weight (after 104 weeks at 100 mg/kg/day p.o., after 13 weeks at 500 mg/kg/day p.o., and after 4 weeks at 20 mg/kg/day i.v.). Kidney weights were reduced after 104 weeks at 100 mg/kg/day p.o., but increased after 26 weeks at 4 or more mg/kg/day p.o. and after 4 weeks at 20 mg/kg/day i.v. Drug-associated, nondose-dependent reductions in liver and thymus weight were observed either in males or females or both in some studies. Though the reductions were, at times, statistically significant, the magnitude of effect was small. Organ weights did not differ from control when high dose animals were allowed a recovery period. The principal drug-related macroscopic findings were erosions and ulcers of the gastric mucosa observed at doses as low as 10 mg/kg/day (as early as 4 weeks). Microscopically, GI ulcer, erosion, inflammation and fibrosis were observed at doses as low as 4 mg/kg/day p.o. in the 26 week study or as low as 10 mg/kg/day p.o. in the 4 week study or at 20 mg/kg/day i.v. Renal pathology consisted of hyperplasia/hypertrophy of the epitheloid cells of the JGA in animals given doses as low as 1 mg/kg/day p.o. for 26 weeks or 50 or more mg/kg/day p.o. for a month or 2 mg/kg/day i.v. Ulcers, erosions and hypertrophy of JGA were reversible over the recovery period in both oral and intravenous dosing studies in rats. All the above effects were found to be less pronounced or largely prevented in animals receiving saline as drinking water.

Dose selection for the rat carcinogenicity study was based on a 3-month dose range-finding dietary study at doses of 10, 30, 100 and 300 mg/kg/day. There were no deaths and no demonstrable clinical signs. The mean body weight gains for treated male groups over the 13 week treatment period were 24 to 32% lower than concurrent control gain. The decrease was dose-dependent. For treated female groups receiving doses of 30 or more mg/kg/day, a dose-dependent reduction in mean body weight gain, 13 to 23% relative to concurrent control (for the 13 week treatment period), was observed. Red blood cell indices decreased 4 to 20% in all drug-treated groups relative to control. Moderate increases in blood urea nitrogen and creatinine were observed in both sexes at all dose levels. Significant organ weight findings included decreased absolute and relative heart weights in all treated groups, and decreased absolute and relative liver weights in males receiving 100 or more mg/kg/day and in females receiving 300 mg/kg/day. The principal drug-related histopathological findings (occurred at all doses) were gastric mucosal ulcers, erosions and/or inflammation and JGA hypertrophy and hyperplasia of the kidney. Based on the above findings, the sponsor concluded that the maximum tolerated dose for the carcinogenicity study was 100 mg/kg/day for both sexes. Doses higher than 100 mg/kg/day administered for more than a year might be expected to result in death due to gastric mucosal ulceration. The sponsor did not seek concurrence from the division prior to initiating the 2-year study.

In the 24-month carcinogenicity study, dietary administration of telmisartan at dose levels up to 100 mg/kg/day elicited no clinical signs of toxicity and did not adversely affect survival. The average achieved doses of telmisartan were within 99.7 to 100.6% of the targeted daily doses. Mean plasma concentrations of telmisartan increased with the dose in both sexes. The 100 mg/kg/day treatment was associated with systemic exposures (AUCs for telmisartan at week 103) that were, on average, 210 (male) and 116- (female) fold higher than those observed in humans at a daily dose of 120 mg. Body weights of males given 15 or more mg/kg/day were significantly lower (4 to 15% less) than control over most of the study period. Females given 15 or more mg/kg/day showed a moderate decrease in body weight (5 to 7%) relative to control during the first 12 study weeks; thereafter, mean body weight differences became less pronounced (0.5 to 6.7%) and from week 60 to study termination, there were no remarkable differences in group mean weights. Red blood cell indices decreased approximately 10 % in high dose males (no change in treated females). Treatment-related biochemical changes (dose-related increases in blood urea nitrogen and creatinine) were most pronounced in mid and high dose males. Histopathology considered to be related to treatment was seen in the kidneys, gastric mucosa, thymus and lymph nodes. Thickening of intralobular renal arteries, an extension of JGA hypertrophy and hyperplasia, and renal cysts were observed in a dose-dependent manner in animals of both sexes receiving 15 or more mg/kg/day. Gastric mucosal injury manifested as erosions and ulcers were noted in both sexes given 15 or more mg/kg/day. Increased incidences of thymic atrophy in high dose males, and cystic ectasia of lymph nodes in mid and high dose males may have been due to body weight gain suppression in these groups. These observations along with reduced body weight gain and increased BUN values in mid and high dose males support the sponsor's decision to consider 100 mg/kg/day as the MTD. Both the sponsor's and the FDA's analyses revealed no statistically significant increased trend in the incidence of any neoplasm that could be attributed to treatment with telmisartan for rats of either sex that survived the treatment period or that were killed or died during the treatment period.

Mice:
The chronic toxicity of telmisartan was evaluated in mice at oral dietary doses of up to 1000 mg/kg/day for 3 (dose range-finding) and 24 months. The mean body weight gains over the 13 week study period were 14% lower for all treated male groups than for the male control group ($p < 0.05$ from week 5 onwards). There were no significant effects on body weight gain for treated females. There were no apparent effects on organ weights, and no drug-related macroscopic or microscopic findings. The highest dose in the 3 month study resulted in a mean AUC value 160-fold greater than that attained at a clinical dose of 120 mg tested in healthy human volunteers. Based on the above, the sponsor selected 1000 mg telmisartan/kg/day as the highest dose for the 2-year carcinogenicity study in this species. The sponsor did not seek concurrence from the division prior to initiating the 2-year study.

In the 24 month study, dietary administration of telmisartan at dose levels up to 1000 mg/kg/day elicited no clinical signs of toxicity. The survival rates for all treated groups were similar to the combined control survival rate. The average achieved telmisartan doses were within 97.6 to 98.6% of the targeted daily doses. The overall mean body weight gain of high dose animals was slightly lower ($p > 0.05$) than the control body weight gain. Mild to moderate anemia was observed in mid and high dose group animals. At terminal sacrifice, the mean absolute and relative liver weights of males and relative liver weight of females given 1000 mg/kg/day were significantly lower than liver weights of diet control but not lactose diet control groups. Absolute and relative kidney and relative adrenal weights were higher in females given 100 or 1000 mg/kg/day than in diet control females. Drug-related histopathology was limited to slight to marked renal hypertrophy/hyperplasia with a higher incidence of renal tubular dilatation in females of all drug treated groups, and a slightly higher incidence of chronic tubulointerstitial nephritis in mid and high dose males. There were no neoplastic findings considered to be related to treatment. Toxicokinetics performed during this study revealed a dosage-related exposure of the animals to telmisartan. Based on the mean AUC values, the systemic exposure at the high dose of 1000 mg/kg/day in the mouse exceeds the human AUC (at a clinical dose of 120 mg) by a factor >200. Thus, it may be concluded that 1000 mg/kg/day, the highest dosage used in this study, was a sufficiently high dosage for evaluation of carcinogenic potential in the CD-1 mouse.

Dogs:
The chronic toxicity of telmisartan was evaluated in dogs at oral doses of up to 500 mg/kg/day for 52 weeks and at intravenous doses of up to 50 mg/kg/day for 4 weeks. The 500 mg/kg/day treatment was associated with systemic exposures (AUCs of telmisartan on day 361) that were, on average, 33- (male) and 46- (female) fold higher than those observed in humans at the maximum recommended daily dose (160 mg). No deaths were associated with oral or iv dosing. Emesis was observed at all doses but frequency was not dose-related. A dose-dependent decrease in body weight was observed for females that received 50 or more mg/kg/day orally, or 5 or more mg/kg/day iv. Notable findings at doses as low as 10 mg/kg/day and as early as 1 month were slight to moderate anemia, JGA hyperplasia/hypertrophy and increases in BUN, creatinine and magnesium. The JGA hyperplasia is considered to represent an unavoidable adaptive response to the desired action of telmisartan on the RAAS and appeared to be reversible (not observed in animals sacrificed after a 6 week recovery period). A treatment-related but non-dose-dependent reduction in heart weight was observed at doses as low as 5 mg/kg/day in the 52 week study only. Renal tubular injury/atrophy as a result of drug treatment was pronounced at

oral doses of 160 mg/kg/day for 4 weeks and 50 or more mg/kg/day for 52 weeks. Another potentially significant adverse effect is GI toxicity. Gastric and/or duodenal mucosal erosions and ulcers, accompanied by slight to mild increases in white blood cell counts, were observed at oral doses of 40 or more mg/kg/day (as early as 4 weeks). Ulcers and erosions healed rapidly after drug withdrawal and were not observed after intravenous dosing (50 mg/kg/day) for 4 weeks in dogs. Under steady state conditions, an intravenous dose of 50 mg/kg/day results in a greater degree of exposure to telmisartan ($AUC_{0\text{-}24h}$ 282 and 338 μg.h/ml, respectively, in males and females) than that observed at an oral dose of 50 mg/kg/day ($AUC_{0\text{-}24h}$ 51 and 47 μg.h/ml, respectively, in males and females). Telmisartan does not appear to have ulcerogenic potential in humans.

Genotoxicity

The genotoxic potential of telmisartan was investigated in a microbial mutagenicity assay (*Salmonella typhimurium* and *E. coli* tester strains), an *in vitro* Chinese hamster lung (V79 cells) mutagenesis assay, an *in vitro* chromosomal aberration assay in human lymphocytes and an *in vivo* assay for clastogenic effects in mouse bone marrow (micronucleus test). Except for the *in vivo* micronucleus test, which relies on intrinsic metabolic capacity, a metabolizing system (S-9 mix derived from Aroclor pretreated rat liver) was used to compensate for the limited metabolizing function of bacteria or mammalian cells in culture. The above test battery failed to implicate telmisartan as possessing mutagenic or clastogenic activity.

Reprotoxicity

In male rats (section 3.5.1), administration of telmisartan (up to 100 mg/kg/day) prior to mating and throughout mating had no effects on mating or fertility indices or on reproductive performance of pregnant F_0 females.

Table 4.1 summarizes telmisartan dosage thresholds for adverse effects observed in all rat and rabbit reprotoxicity studies other than effects in F_0 males in the fertility study. Administration of telmisartan to female rats (up to 100 mg/kg/day) from 2 weeks prior to mating until day 6 of gestation did not produce adverse effects on fertility or reproductive performance. No maternal deaths were observed in any of the rat studies. However, telmisartan doses of 5 or more mg/kg/day were associated with significant decreases in maternal body weight gain, and doses of 15 or more mg/kg/day were associated with significant decreases in food consumption. Telmisartan (up to 50 mg/kg/day) did not affect fetal survival or fetal weight when administered to rats during organogenesis (gestation days 7 to 16); nor did it affect the development of F_1 pups. However, when treatment was continued through lactation, there was reduced viability, low birth weight, decreased weight gain (all at doses of 15 or more mg/kg/day) and delayed maturation of pups [delayed eye opening (at 50 mg/kg/day) and incisor eruption (at 5 or more mg/kg/day)] (Table 4.1). Like other drugs acting on the RAAS, the critical period for adverse developmental effects in the rat appears to be late gestation and/or lactation.

TABLE 4.1
DOSAGE THRESHOLDS* FOR ADVERSE EFFECTS OF TELMISARTAN IN RAT AND RABBIT REPRODUCTION STUDIES

Test #/Review section #	95-2031/3.5.1	93-2079/3.5.2	97-2107/3.5.3	94-2119/3.5.4
Species (strain)	Rat (THOM)	Rat (THOM)	Rat (THOM)	Rabbit (HM)
Doses (mg/kg/day by gavage)	5, 15, 100	5, 15, 50	5, 15, 50	5, 15, 45
Days of drug administration	See below [a]	GDs 7-16	GD 6 - LD 21	GDs 6-18
Day of necropsy	GD 14-16	GD 22, LD 22	LD 22	GD 29
Maternal Toxicity				
1. Mortality	>100	>50	>50	15-45[g]
2. ↓ weight gain	<5[b]	<5[d]	<5[e]	15-45
3. ↓ food intake	15-100[c]	<5	<5[f]	15-45
Embryo/Fetal Toxicity				
1. ↓ survival	>100	>50	>50	15-45[h]
2. ↓ fetal weight /pup birth weight	Not applicable	>50	15-50	>45
Neonatal Toxicity				
1. ↓ survival	Not applicable	>50	5-15	Not applicable
2. ↓ body weight gain		>50	5-15	
3. Postnatal development				
delayed eye opening		>50	15-50	
delayed incisor eruption		>50	<5	

Wistar derived;

*When two doses are given, the first is the highest dose at which an effect was not seen and the second is the lowest dose at which an effect was seen.

a: 14 days prior to mating with treated males, during mating and until day 6 of gestation

b: maximum decrease ($p < 0.05$) for all groups on GD 6. The high dose group recovered slowly with time but decrease still significant on the day of necropsy.

c: on GD 6 only

d: $p < 0.05$ at all dose levels on GD 16, $p < 0.05$ at high dose on GD 21

e: significant reduction from GD 9 to GD 22 in mid and high dose groups, significant in low dose group from GD 11 to GD 13

f: throughout gestation and lactation in mid and high dose groups only

g: one of 16 high dose animals died (on GD 21); cause of death not determined

h: increase in post-implantation loss and decrease in viable fetuses due to total resorptions in 5 of 16 high dosage does.

Telmisartan is transferable to the embryo-fetal compartment. The concentration of telmisartan in the rat placenta on the 12th or 18th day of gestation (determined in single dose study) is about 1/3rd of that in the maternal blood. The concentration in the amniotic fluid increased with time and surpassed the maternal blood level at its peak (48 hr postdose). Distinct concentrations of radioactive telmisartan were found in the whole fetus and the fetal liver, fetal kidney and fetal lung 4 hr after administration of test drug (earliest sampling time). These levels were higher 24 hr post dose, exceeding the maternal blood levels at that time and were still relatively high 48 hr post dose. Transfer of ^{14}C-telmisartan into the milk in the rat was slow; maximum mean ^{14}C concentrations were observed in both plasma and milk 8 hr after administration of radioactive

test substance. The concentration of radioactivity in milk was about 1.5 to 2 times higher than in plasma.

Pregnancy did not alter the pharmacokinetic profile of telmisartan in rats. Maternal C_{max} and AUC values obtained in pregnant animals were not remarkably different from values obtained over a similar dose range in non-pregnant rats in repeated dose toxicity studies. No adverse effects on male or female fertility or reproductive performance would be expected in men or women receiving therapeutic doses of telmisartan (mean AUC at 100 mg/kg/day in rat is approximately 51 times the mean AUC in human trials at 120 mg).

Like other drugs acting on the RAAS, telmisartan produced marked toxicity in the pregnant rabbit. Maternal toxicity manifested as death (in 1/16 does) and reduced body weight gain and food consumption occurred at 45 mg/kg/day. This dose also resulted in reduced embryo/fetal survival with complete resorption seen in 5/16 rabbits. Weights of fetuses surviving to c-section were unaffected. No teratogenic potential was observed with telmisartan in rabbits (up to 45 mg/kg/day with saline supplementation) or rats (up to 50 mg/kg/day).

Mean AUC at 15 mg/kg/day in rabbit is 16 times the mean AUC in clinical trials at 120 mg.

5. LABELING

Those sections in the proposed labeling (version 6/18/98) that refer to preclinical studies were reviewed and the following changes are recommended:

The sponsor's proposed text summarizing the results of studies in rats and rabbits (line nos. 172 to 181) reads as follows:

Redacted 1

pages of trade secret and/or confidential commercial information

6. RECOMMENDATIONS

This new drug application for telmisartan is approvable with recommended changes in labeling

/S/

G. Jagadeesh, Ph.D.

cc:
Original NDA 20,850 (Telmisartan)
HFD-110
HFD-110/CSO
HFD-124/J. DeGeorge
HFD-345/
Accepted by: CAM 8-17-98

GJ/8/14/98/NDA20850 TELMISARTAN.DOC